Exploration of tricyclic heterocycles as core structures for RIOK2 inhibitors

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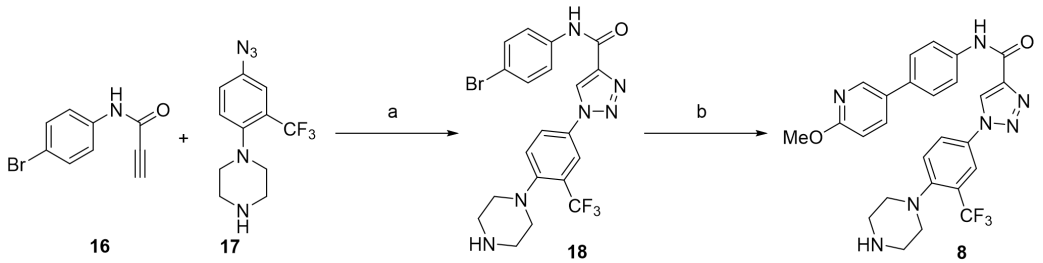
Supporting Information

General Information.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-400 or 500 MHz spectrometer. Coupling constants, *J*, were reported in hertz (Hz). High-resolution mass spectra (HRMS) were obtained using a Q-STAR Elite ESI-LC−MS/MS spectrometer. Chemical names were generated using Cambridge Soft. ChemDraw Ultra 16.0. Commercially obtained reagents were used without further purification. All compounds are >95% pure by high-performance liquid chromatography analysis.

General Procedure for preparation of 8.

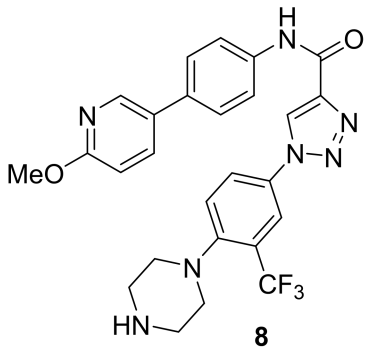


16 17 18 8

Scheme 1. Synthesis of compound **8**: (a) CuI, DMSO, 90 °C; (b) 2-methoxy-5-pyridine boronic acid (**19**), $Pd(PPh_3)_4$ Cs_2CO_3, DMF/H_2O, 80 °C.

Synthesis of compound 18: The mixture of compound **16** (1.5 g, 6.7 mmol), **17** (1.8 g, 6.7 mmol) and CuI (0.12 g, 0.67 mmol) in dimethyl sulfoxide (DMSO) (10 mL) was heated at 90 °C under argon for 4 h. After the reaction was complete, 28% aqueous ammonia (2 mL) and water (20 mL) were added into the reaction mixture. The mixture was then extracted with CH_2Cl_2 (50 mL × 3) and washed with brine and water. The organic layer was combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was directly used for the next step.

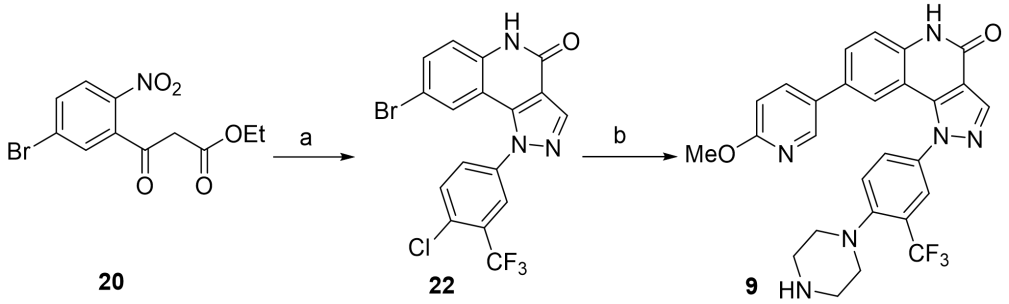
Synthesis of compound 8: Compound **18** (0.6 g, 1.21 mmol), 2-methoxy-5-pyridine boronic acid (0.28 g, 1.82 mmol), $Pd(PPh_3)_4$ (28 mg, 0.024 mmol) and Cs_2CO_3 (0.79 g, 2.43 mmol) in DMF/H_2O (3:1, 12 mL) were heated at 80 °C under argon overnight. After the reaction was completed, the reaction solution was quenched with water. The mixture was filtered, and the solid was further purified through flash chromatography (DCM/MeOH/Et_3N = 100:10:1) on silica gel to afford compound **8** as a white solid. 71% yield.



8

N-(4-(6-methoxypyridin-3-yl)phenyl)-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)-1H-1,2,3-triazole-4-carboxamide (8): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.72 (s, 1H), 9.56 (s, 1H), 8.49 (dd, J = 2.6, 0.8 Hz, 1H), 8.28-8.26 (m, 2H), 8.02 (dd, J = 8.6, 2.4 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 9.2 Hz, 1H), 7.67 (d, J = 8.8 Hz, 2H), 6.90 (dd, J = 8.8, 0.4 Hz, 1H), 3.89 (s, 3H), 2.77-2.87 (m, 8H). ^{13}C NMR (100MHz, DMSO-d_6) δ 162.9, 158.0, 153.1, 144.3, 143.8, 137.9, 137.2, 132.4, 128.9, 126.6, 126.5, 126.5, 126.4 (q, J = 5.0 Hz), 126.1 (q, J = 29.0 Hz), 125.7, 124.8, 122.1, 121.0, 121.0, 119.9 (q, J = 272.0 Hz), 110.6, 54.0, 53.3, 45.7. HRMS m/z: Calcd. for $C_{26}H_{25}F_3N_7O_2$ $[M+H]^+$ 524.2016. Found 524.2013. Purity 98.6% by HPLC.

General Procedure for preparation of 9.



Scheme 2. Synthesis of compound **9**: a) (i) DMF-DMA, PhMe, reflux, 4 h; (ii) (4-Chloro-3-(trifluoromethyl) phenyl) hydrazine hydrochloride (**21**), EtOH, reflux; (iii) Fe, NH_4Cl, EtOH/H_2O, 80 ℃; (iv) HCl, MeOH, 70 ℃; b) (i) 2-methoxy-5-pyridine boronic acid (**19**), $Pd(PPh_3)_4$, Cs_2CO_3, DMF/H_2O, 80 ℃; (ii) piperazine, $Pd_2(dba)_3$, RuPhos, *t*BuOK, dioxane, 120 ℃.

Synthesis of compound 22: Compound **20** (1.6 g, 5.06 mmol) and DMF-DMA (3.36 ml, 25.31 mmol) in PhMe (20 mL) were heated at 120 ℃ for 4h. After the reaction was completed, the reaction solution was cooled to room temperature and the solvent was removed to obtain a crude product which was used directly for the next step.

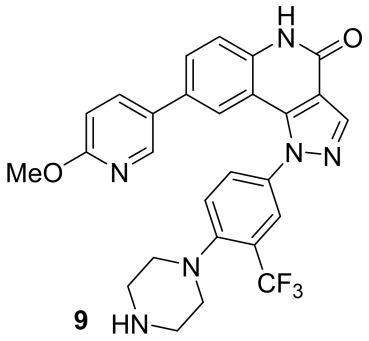
The above crude product (1.88g, 5.1 mmol) and (4-Chloro-3-(trifluoromethyl) phenyl) hydrazine hydrochloride (1.25 g, 5.1 mmol) in EtOH (20 mL) were heated at 80 °C overnight. After the reaction was completed, the reaction solution was filtered, and the precipitate was dried to obtain a crude product which was used directly for the next step.

The above crude product (2 mmol), Fe (556 mg, 10 mmol) and NH_4Cl (856 mg, 16 mmol) in EtOH/H_2O (4:1, 50 mL) were heated at 80 °C overnight. After the reaction was completed, the reaction solution was filtered by infusorial silica, and the pH was adjusted to 8.0 with Na_2CO_3. The mixture was extracted with CH_2Cl_2 (100 mL × 3) and washed with brine and water. The organic layer was combined, dried over Na_2SO_4, and concentrated in vacuo to obtain a crude product which was used directly for the next step.

The above crude product (0.5 g, 1.01 mmol) and HCl (12 mmol) in EtOH (10 mL) were heated at 80 °C overnight. After the reaction was completed, the reaction solution was filtered, and the precipitate was dried to obtain a crude product **22** which was used directly for the next step.

Synthesis of compound 9: Compound **22** (0.44 g, 1.0 mmol), 2-methoxy-5-pyridine boronic acid (0.23 g, 1.5 mmol), $Pd(PPh_3)_4$ (20 mg, 0.02 mmol) and Cs_2CO_3 (0.65 g, 2.00 mmol) in DMF/H_2O (3:1, 12 mL) were heated at 80 °C under argon overnight. After the reaction was completed, it was quenched with water. The mixture was filtered, and the solid was directly used for the next step.

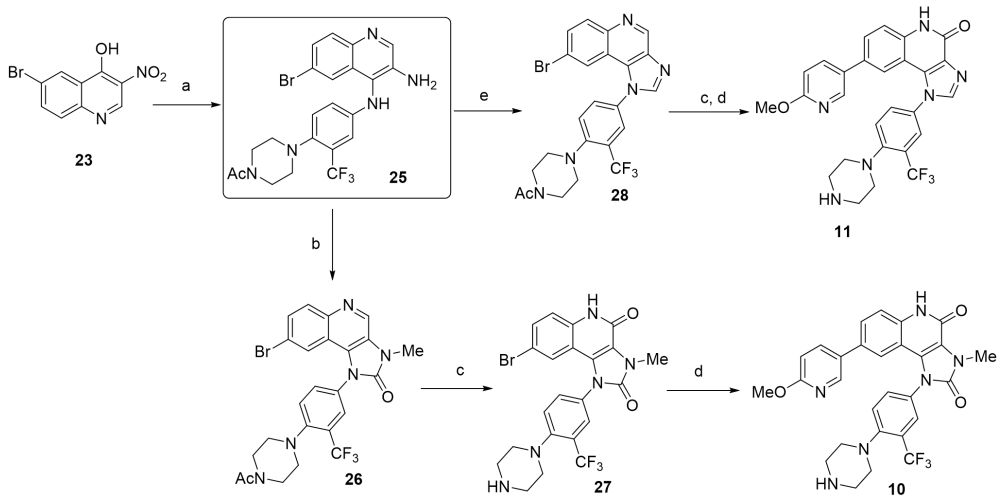
The above crude product (0.47 g, 1 mmol), piperazine (0.34 g, 4 mmol), *t*BuOK (0.22 g, 2 mmol), $Pd_2(dba)_3$ (9 mg, 0.01 mmol) and RuPhos (9 mg, 0.02 mmol) in dioxane (10 mL) were heated at 120 °C under argon overnight. After the reaction was completed, the reaction solution was quenched with water. The mixture was filtered, and the solid was further purified through flash chromatography (DCM/MeOH/Et_3N = 100:10:1) on silica gel to afford compound **9** as a white solid. 38% yield.



9

8-(6-methoxypyridin-3-yl)-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)-1,5-dihydro-4H-pyrazolo[4,3-c]quinolin-4-one (9): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, 1H), 8.43 (s, 1H), 8.09-8.14 (m, 3H), 7.83-7.90 (m, 2H), 7.64 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.05 (s, 1H), 6.84 (d, J = 8.4 Hz, 1H), 3.85 (s, 3H), 3.17-3.27 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.0, 157.9, 153.5, 143.8, 140.6, 137.8 (q, J = 5.0 Hz), 136.5, 136.2, 133.0, 129.9, 128.0 (q, J = 29.0 Hz), 126.8 (q, J = 272.0 Hz), 126.5, 126.3, 126.0, 124.2, 122.4, 119.0, 117.4, 114.1, 110.6, 110.4, 53.2, 52.4, 44.8. HRMS calcd for $C_{27}H_{24}F_3N_6O_2^+$ $(M+H)^+$ 521.1907, found 521.1909. Purity 97.4% by HPLC.

General Procedure for preparation of 10 and 11.



Scheme 3. Syntheses of compounds 10 and 11: a). (i) $POCl_3$, 110 ℃; (ii) 1-(4-(4-amino-2-(trifluoromethyl)phenyl)piperazin-1-yl)ethan-1-one (**24**), AcOH, rt; (iii) Fe, NH_4Cl, EtOH/H_2O, 80 ℃; b) (i) CDI, THF, 60 ℃; (ii) MeI, NaH, DMF, 25 ℃; (c) (i) *m*-CPBA, DCM, 0 ℃; (ii) Ac_2O, 140 ℃; (iii) 30% hydrochloric acid, 120 ℃; (d) 2-methoxy-5-pyridine boronic acid (**19**), $Pd(PPh_3)_4$, Cs_2CO_3, DMF/H_2O, 80 ℃; (e) triethyl orthoformate, 150 ℃.

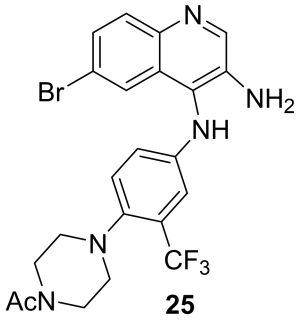
Synthesis of compound 10:

Compound **23** (5 g, 18.59 mmol) in $POCl_3$ (20 mL) was refluxed for 4 h at 110 °C . After the reaction was completed, the reaction solution was cooled to 0 ℃ and quenched with ice water. The mixture was added $NaHCO_3$ to adjust pH to 8.0, and extracted with ethyl acetate (100 mL × 3) and washed with brine and water. The organic layer was combined, dried over Na_2SO_4, and concentrated in vacuo to obtain a crude product which was used directly for the next step.

The above crude product (2.88 g, 10 mmol) and 1-(4-(4-amino-2-(trifluoromethyl) phenyl)piperazin-1-yl)ethan-1-one (3.45 g, 12 mmol) in AcOH (30 mL) were stirred for 3 h at room temperature. After the reaction was complete, the reaction solution was quenched with water and extracted with CH_2Cl_2 (100 mL × 3) and washed with brine and water. The organic layer was combined, dried over Na_2SO_4, and concentrated in vacuo to obtain a crude product which was used directly for the next step.

The above crude product (2 mmol), Fe (556 mg, 10 mmol) and NH_4Cl (856 mg, 16 mmol) in EtOH/H_2O (4:1, 50 mL) were heated at 80 °C overnight. After the reaction was complete, the reaction solution was filtered by infusorial silica, and the pH was adjusted to 8.0 with Na_2CO_3. The mixture was extracted with CH_2Cl_2 (100

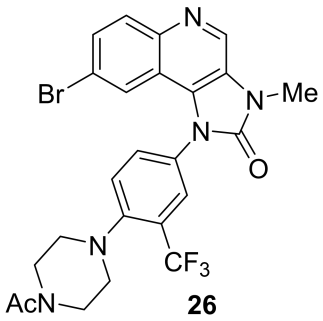
mL × 3) and washed with brine and water. The organic layer was combined, dried over Na_2SO_4, and concentrated in vacuo to obtain compound **25** as a yellow solid. 91% yield.



25

1-(4-(4-((3-amino-6-bromoquinolin-4-yl)amino)-2-(trifluoromethyl)phenyl)piperazin-1-yl)ethan-1-one (25): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.60 (s, 1H), 7.90 (d, J = 2.4 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.51 (dd, J = 9.0 Hz, 2.2 Hz, 1H), 7.13 (d, J = 8.6 Hz, 1H), 6.98 (d, J = 2.8 Hz, 1H), 6.64 (dd, J = 8.6 Hz, 2.8 Hz, 1H), 6.27 (s, 1H), 4.16 (s, 2H), 3.91-3.57 (m, 2H), 3.48-3.54 (m, 2H), 2.82 (t, J = 4.8 Hz, 2H), 2.76 (t, J = 4.8 Hz, 2H), 2.11 (s, 3H).

Compound **25** (2.6 g, 5.1 mmol) and CDI (1.66 g, 10.2 mmol) in THF (20 mL) were heated to 60 ℃ overnight. After the reaction was completed, the reaction solution was filtered, and the precipitate was washed with THF and dried to obtain a crude product for the next step. The obtained intermediate (1.73 g, 3.3 mmol) and NaH (0.4 g, 9.9 mmol) in DMF (20 mL) were stirred 20min at rt. The reaction solution was added CH_3I (1.02 g, 7.2 mmol) at 0 ℃ and stirred 5 h at rt. After the reaction was completed, the reaction solution was quenched with water and filtered. The precipitate was dried to obtain compound **26** as a white solid. 92% yield.



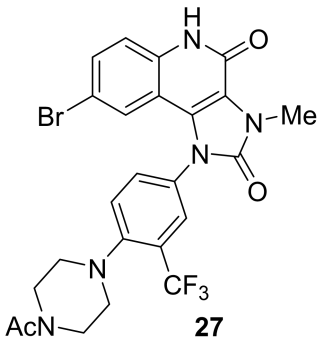
26

1-(4-(4-acetylpiperazin-1-yl)-3-(trifluoromethyl)phenyl)-8-bromo-3-methyl-1,3-dihydro-2H-imidazo[4,5-c]quinolin-2-one (26): ^{1}H NMR (400 MHz, DMSO-d_6) δ

9.06 (s, 1H), 8.08-8.02 (m, 1H), 8.00-7.93 (m, 2H), 7.87-7.85 (m, 1H), 7.68-7.66 (m, 1H), 6.98-6.96 (m, 1H), 3.68-3.60 (m, 4H), 3.60 (s, 3H), 3.05-3.00 (m, 2H), 2.99-2.92 (m, 2H), 2.07 (s, 3H).

Compound **26** (0.55 g, 1 mmol) and *m*-CPBA (0.27 g, 1.1 mmol) in DCM (10 mL) were stirred at room temperature overnight. After the reaction was completed, the pH was adjusted to 8.0 with NaOH. The mixture was extracted with CH_2Cl_2 (50 mL x 3) and washed with brine and water. The organic layer was combined, dried over Na_2SO_4, and concentrated in vacuo to obtain a crude product for the next step. The obtained intermediate (0.06 g, 0.1 mmol) in Ac_2O (1 mL) was refluxed for 1 h at 140 ℃. After the reaction was completed, the reaction solution was concentrated in vacuo and washed with EA/PE (1:1, 10 mL), and filtered to obtain a crude product for the next step.

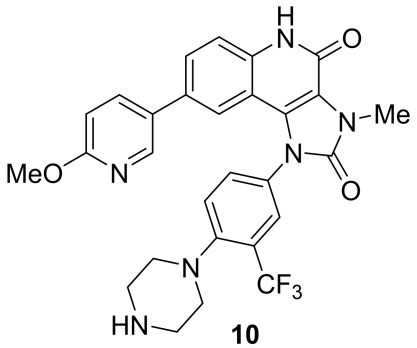
The above crude product (0.05 g. 0.1 mmol) in HCl/H_2O (1:1, 10 mL) was heated to 120 ℃ overnight. After the reaction was completed, the reaction solution was added NaOH (aq) to adjust PH to 8.0. The mixture was extracted with CH_2Cl_2 (50 mL x 3) and washed with brine and water. The organic layer was combined, dried over Na_2SO_4, and concentrated in vacuo to obtain compound **27** as a white solid. 95% yield.



27

8-bromo-3-methyl-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)-3,5-dihydro-1H-imidazo[4,5-c]quinoline-2,4-dione (27): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (s, 1H), 8.01 (d, J = 2.4 Hz, 1H), 7.93 (dd, J = 8.4, 2.4 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.52 (dd, J = 8.8, 2.0 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 6.53 (d, J = 2.0 Hz, 1H), 3.66 (s, 3H), 3.19-3.08 (m, 8H).

Compound **27** (0.05 g, 0.1 mmol), 2-methoxy-5-pyridine boronic acid (0.02 g, 0.15 mmol), $Pd(PPh_3)_4$ (2.3 mg, 0.002 mmol) and Cs_2CO_3 (0.13 g, 0.4 mmol) in DMF/H_2O (3:1, 4 mL) were heated at 80 °C under argon overnight. After the reaction was completed, it was quenched with water. The mixture was filtered, and the solid was further purified through flash chromatography (DCM/MeOH/Et_3N = 100:10:1) on silica gel to afford compound **10** as a white solid. 85% yield.

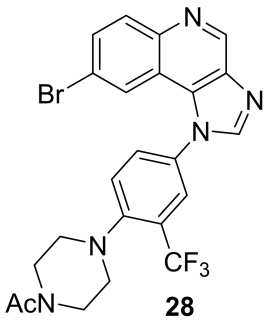


10

8-(6-methoxypyridin-3-yl)-3-methyl-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)-3,5-dihydro-1H-imidazo[4,5-c]quinoline-2,4-dione (10): ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.04 (s, 1H), 8.03 (d, J = 2.4 Hz, 1H), 7.95 (dd, J = 8.4, 2.4 Hz, 1H), 7.90 (d, J = 2.4 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.70 (dd, J = 8.4, 2.0 Hz, 1H), 7.58 (dd, J = 8.4, 2.4 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.63 (d, J = 2.0 Hz, 1H), 3.83 (s, 3H), 3.68 (s, 3H), 3.02-2.95 (m, 8H).^{13}C NMR (100 MHz, DMSO-d_6) δ 163.1, 153.7, 153.2, 143.8, 136.7, 135.4, 134.8, 131.8, 130.1, 128.5, 128.3, 128.1, 126.4, 126.3 (q, J = 5.0 Hz), 126.2 (q, J = 30.0 Hz), 126.1, 124.4, 122.6, 117.4, 114.6 (q, J = 272.0 Hz), 110.7, 110.5, 53.4, 53.3, 45.4, 29.3. HRMS calcd for $C_{28}H_{26}F_3N_6O_3^+$ $(M + H)^+$ 551.2013, found 551.1992 . Purity 99.6% by HPLC.

Synthesis of compound 11:

Compound **25** (0.6 g, 1.18 mmol) in triethyl orthoformate (12 mL) was refluxed for 3 h at 150 ℃. After the reaction was completed, the reaction solution was concentrated in vacuo and the crude product was further purified through flash chromatography (DCM/MeOH = 10:1) on silica gel to afford compound **28** as a white solid. 82% yield.



28

1-(4-(4-(8-bromo-1H-imidazo[4,5-c]quinolin-1-yl)-2-(trifluoromethyl)phenyl)piperazin-1-yl)ethan-1-one (28): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.28-8.03 (m, 2H), 7.89-7.81 (m, 1H), 7.79-7.70 (m, 2H), 7.68-7.61 (m, 1H), 7.50-7.44 (m, 1H), 3.87-3.65 (m, 4H), 3.19-3.01 (m, 4H), 2.16 (s, 3H).

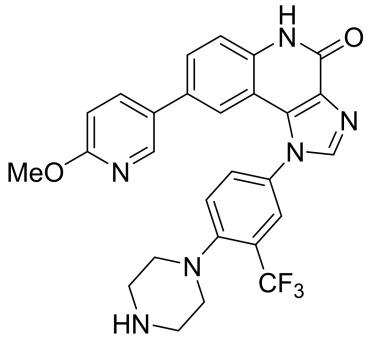
Compound **28** (0.52 g, 1 mmol) and *m*-CPBA (0.27 g, 1.1 mmol) in DCM (10 mL) were stirred at room temperature overnight. After the reaction was completed, the pH was adjusted to 8.0 with NaOH. The mixture was extracted with CH_2Cl_2 (50 mL x 3) and washed with brine and water. The organic layer was combined, dried over Na_2SO_4, and concentrated in vacuo to obtain a crude product for the next step.

The above product (0.26 g, 0.5 mmol) in Ac_2O (5 mL) was refluxed for 1 h at 140 ℃. After the reaction was completed, the reaction solution was concentrated in vacuo and washed with EA/PE (1:1, 10 mL) to obtain a crude product which was used directly for the next step.

The above product (0.21 g. 0.4 mmol) in HCl/H_2O (1:1, 10 mL) was heated to 120 ℃ overnight. After the reaction was completed, the solution was added NaOH solution to adjust PH to 8.0. The mixture was extracted with CH_2Cl_2 (50 mL x 3) and washed with brine and water. The organic layer was combined, dried over Na_2SO_4, and concentrated in vacuo to obtain a crude product which was used directly for the next step.

The above product, 2-methoxy-5-pyridine boronic acid (0.02 g, 0.15 mmol), Pd $(PPh_3)_4$ (2.3 mg, 0.002 mmol) and Cs_2CO_3 (0.13 g, 0.4 mmol) in DMF/H_2O (3:1, 4 mL) were heated at 80 °C under argon overnight. After the reaction was completed, the reaction solution was quenched with water. The mixture was filtered, and the

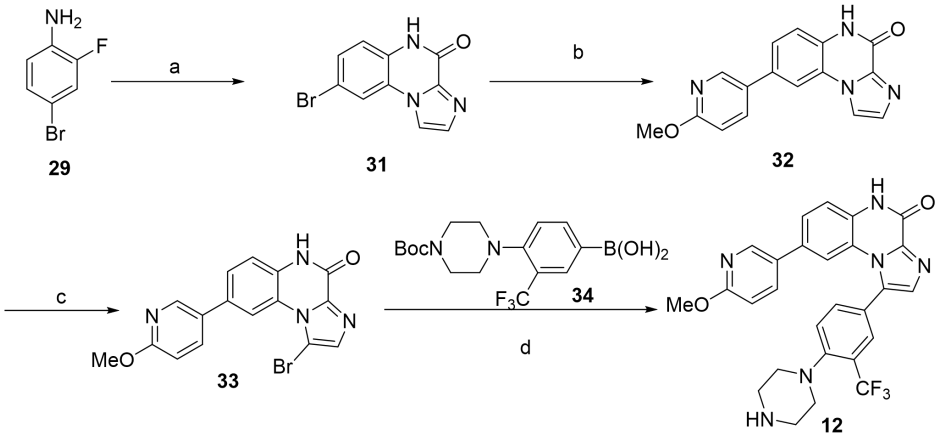
solid was further purified through flash chromatography (DCM/MeOH/Et_3N = 100:10:1) on silica gel to afford compound **11** as a white solid. 70% yield.



11

8-(6-methoxypyridin-3-yl)-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)-1,5-dihydro-4H-imidazo[4,5-c]quinolin-4-one (11): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 1H), 8.38 (s, 1H), 8.15 (d, J = 2.4 Hz, 1H), 8.06 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.98 (d, *J* = 2.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.72 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.60 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 6.84 (d, *J* = 1.6 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 3.83 (s, 3H), 3.08-3.00 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.9, 157.5, 154.4, 143.7, 142.8, 136.6, 136.4, 134.2, 133.2, 132.2, 131.8, 129.6, 128.3, 127.1(q, *J* = 5.0 Hz), 126.4 (q, *J* = 29.0 Hz), 126.1, 122.5 (q, *J* = 272.0 Hz), 117.5, 117.1, 114.5, 111.7, 110.5, 54.2, 53.1, 45.7. HRMS calcd for $C_{27}H_{24}F_3N_6O_2^+$ $(M + H)^+$ 521.1907, found 521.1909. Purity 99.2% by HPLC.

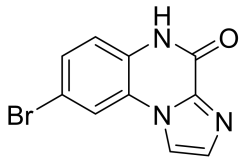
General Procedure for preparation of 12.



Scheme 4. Synthesis of compounds **12**: a) (i) 1H-imidazole-2-carboxylic acid (**30**), HOBt, EDCI; (ii) NaH, DMA, 80 ℃; b) 2-methoxy-5-pyridine boronic acid (**19**), $Pd(PPh_3)_4$ Cs_2CO_3, DMF/H_2O, 80 ℃; c) NBS, DMF, 80 ℃; d) (i) $PdCl_2(PPh_3)_2$, Cs_2CO_3, DMF/H_2O, 80 ℃; (ii) TFA, DCM, 25 ℃.

Synthesis of compound 31: Compound **29** (3.95 g, 35.27 mmol)， 1H-imidazole -2-carboxylic acid (6.7 g, 35.27 mmol), HOBt (7.15 g, 52.91 mmol) and EDCI (10.14 g, 52.91 mmol) in DMF (100 mL) were stirred at room temperature overnight. After the reaction was completed, The reaction solution was extracted with ethyl acetate (150 mL x 3) and washed with brine and water. The organic layer was combined, dried over Na_2SO_4, and concentrated in vacuo. The crude product was further purified through flash chromatography (DCM) on silica gel to obtain a crude product which was used directly for the next step.

The above product (2.7 g, 9.5 mmol) and NaH (50 mg, 12.4 mmol) in DMA (40 mL) were refluxed at 170 ℃ overnight. After the reaction was completed, the reaction solution was quenched with water. The mixture was filtered, and the solid was further purified through flash chromatography (DCM/MeOH = 10:1) on silica gel to afford compound **31** as a white solid. 95% yield.



31

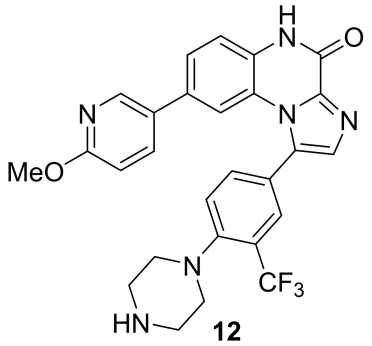
8-bromoimidazo[1,2-a]quinoxalin-4(5H)-one (31): ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H), 8.62-8.58 (m, 1H), 8.46-8.42 (m, 1H), 7.62-7.54 (m, 2H), 7.33-7.29 (m, 1H).

Synthesis of compound 32: Compound **31** (1.71 g, 6.48 mmol), Compound **19** (1.46 g, 9.72 mmol), $Pd(PPh_3)_4$ (150 mg, 0.13 mmol) and Cs_2CO_3 (6.3 g, 19.44 mmol) in DMF/H_2O (3:1, 40 mL) were heated at 80 °C under argon overnight. After the reaction was completed, the reaction solution was filtered, and the residue **32** was used directly for the next step.

Synthesis of compound 33: The above product **32** (1.44 g, 4.93 mmol) and NBS (1.32 g, 7.39 mmol) in DMF (60 mL) were heated to 80 ℃ overnight. After the reaction was completed, the reaction solution was filtered, and the precipitate was dried to obtain a crude product **33** which was directly used for the next step.

Synthesis of compound 12: Compound **33** (0.57 g, 1.54 mmol), compound **34** (0.87 g, 2.31 mmol), $Pd(PPh_3)Cl_2$ (108 mg, 0.15 mmol) and Cs_2CO_3 (1.5 g, 4.62 mmol) in DMF/H_2O (3:1, 20 mL) were heated at 80 °C under argon overnight. After the reaction was completed, the reaction solution was filtered, and the residue was further purified through flash chromatography (DCM/MeOH = 50:1) on silica gel to obtain a crude product which was used directly for the next step.

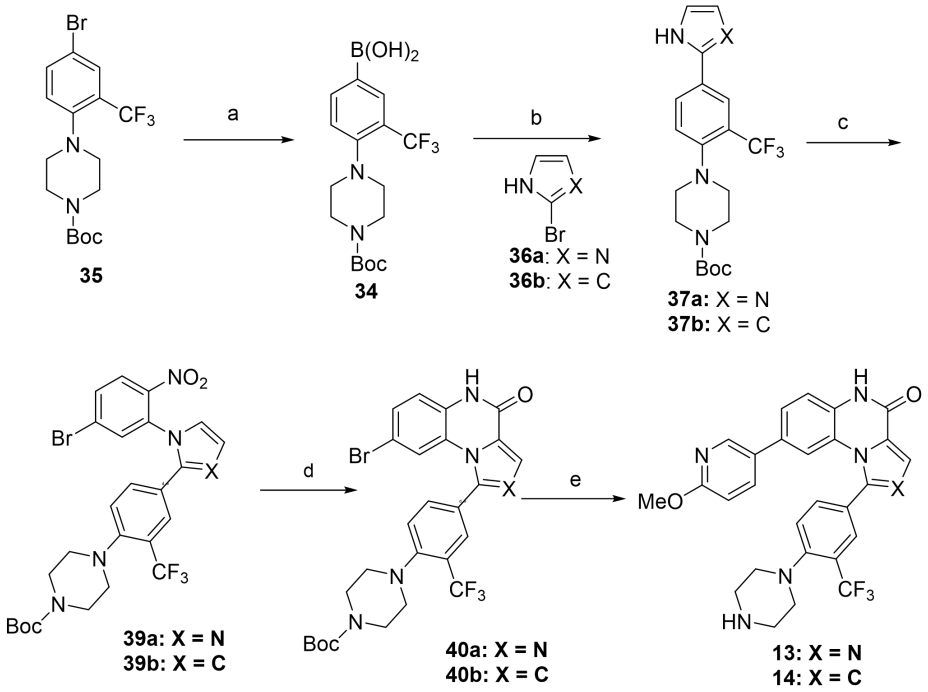
The above product (350 mg, 0.56 mmol) and TFA (6.4 g, 56 mmol) in DCM (5 mL) were stirred at 25 ℃ overnight. After the reaction was completed, the reaction solution was concentrated in vacuo. The pH was adjusted to 8.0 with Na_2CO_3, and the mixture was filtered, and the residue was further purified through flash chromatography (DCM/MeOH = 5:1) on silica gel to afford compound **12** as a white solid. 90% yield.



12

8-(6-methoxypyridin-3-yl)-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)imidazo[1,2-a]quinoxalin-4(5H)-one (12): ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.02 – 7.91 (m, 2H), 7.87-7.75 (m, 2H), 7.66-7.61 (m, 2H), 7.59-7.53 (m, 1H), 7.46-7.40 (m, 1H), 7.06 (s, 1H), 6.79-7.72 (m, 1H), 3.82 (s, 3H), 3.20-3.00 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.0, 152.9, 152.6, 143.7, 137.7, 136.5, 135.8, 133.2, 130.3, 129.6, 129.3 (q, J = 5.0 Hz), 128.6, 127.8, 127.0, 125.9(q, J = 30.0 Hz), 125.3, 125.0 (q, J = 272.0 Hz), 124.4, 123.0, 117.7, 113.6, 110.6, 53.1, 52.0, 44.6. HRMS calcd for $C_{27}H_{24}F_3N_6O_2^+$ $(M + H)^+$ 521.1907, found 521.1887. Purity 99.5% by HPLC.

General Procedure for preparation of 13 and 14.



Scheme 5. Syntheses of compounds **13** and **14**: a) *n*-BuLi, $B(OEt)_3$; b) $PdCl_2(PPh_3)_2$, Cs_2CO_3, DMF/H_2O, 80 °C; c) 2-fluoro-4-bromonitrobenzene (**38**), Cs_2CO_3, DMSO; d) (i) Fe, NH_4Cl, $EtOH/H_2O$, 80 °C; (ii) CDI, *o*-dichlorobenzene, reflux; e) (i) 2-methoxy-5-pyridine boronic acid (**19**), $Pd(PPh_3)_4$, Cs_2CO_3, DMF/H_2O, 80 °C; (ii) TFA, DCM, 25 °C.

Synthesis of compound 34: Compound **35** (10.3 g, 25.18 mmol) in PhMe/THF (1:1, 100 mL) was added *n*-BuLi (37.77 mmol) slowly at -78°C. The mixture was stirred for 1 h and added $B(OEt)_3$ (5.52 g, 37.77 mmol) at -78°C. After the reaction was completed, the reaction solution was added NH_4Cl (40 mL) and extracted with ethyl acetate (100 mL × 3) and washed with brine and water. The organic layer was combined, dried over Na_2SO_4, and concentrated in vacuo to obtain a crude product which was used directly for the next step.

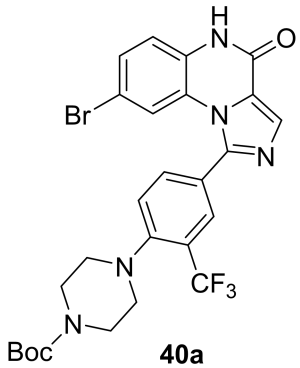
Synthesis of compound 37a/37b: Compound **34** (1 g, 2.67 mmol), compound **36a**/**36b** (2.23 mmol), $Pd(PPh_3)Cl_2$ (156 mg, 0.22 mmol) and Cs_2CO_3 (1.45 g, 4,46 mmol) in DMF/H_2O (3:1, 20 mL) were heated at 80 °C under argon overnight. After the reaction was completed, the reaction solution was quenched with water. The mixture was filtered, and the solid was further purified through flash chromatography ($DCM/MeOH/Et_3N$ = 100:10:1) on silica gel to obtain a crude product which was used directly for the next step.

Synthesis of compound 39a/39b: Compound **37a**/**37b** (2 mmol), 2-fluoro-4-

bromonitrobenzene (528 mg, 2.4 mmol) and Cs_2CO_3 (984 mg, 3 mmol) in DMSO were stirred at room temperature overnight. After the reaction was completed, the reation solution was quenched with water. The mixture was extracted with CH_2Cl_2 (50 mL x 3) and washed with brine and water. The organic layer was combined, dried over Na_2SO_4, and concentrated in vacuo to obtain a crude product which was used directly for the next step.

Synthesis of compound 40a/40b: Compound **39a/39b** (2 mmol), Fe (556 mg, 10 mmol) and NH_4CI (856 mg, 16 mmol) in EtOH/H_2O (4:1, 50 mL) were heated at 80 °C overnight. After the reaction was complete, the reaction solution was filtered by infusorial silica, and the pH was adjusted to 8.0 with Na_2CO_3. The mixture was extracted with CH_2Cl_2 (100 mL × 3) and washed with brine and water. The organic layer was combined, dried over Na_2SO_4, and concentrated in vacuo to obtain a crude product which was used directly for the next step.

The above product (1.8 mmol ） and CDI (350 mg, 2.2 mmol) in *o*-dichlorobenzene (20 mL) were refluxed at 190 ℃ overnight. The reaction solution was purified through flash chromatography (EA/PE = 3:1) on silica gel to afford compound **40a/40b** as a white solid. 55% yield.



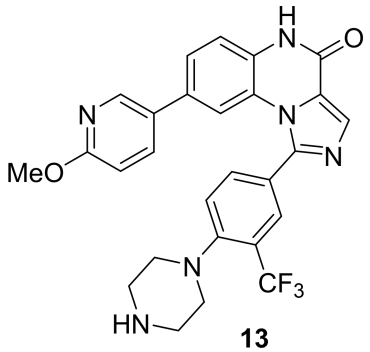
40a

tert-butyl-4-(4-(8-bromo-4-oxo-4,5-dihydroimidazo[1,5-a]quinoxalin-1-yl)-2-(trifluoromethyl)phenyl)piperazine-1-carboxylate (40a): ^{1}HNMR (400MHz, DMSO-d_6) δ 11.60 (s, 1H), 8.02 (s, 1H), 8.00-7.93 (m, 2H), 7.83-7.75 (m,, 1H), 7.50-7.42 (m, 1H), 7.30-7.22 (m, 1H), 7.08-7.00 (m, 1H), 3.57-3.45 (m, 4H), 3.02-2.90 (m, 4H), 1.44 (s, 9H).

Synthesis of compound 13/14: Compound **40a**/**40b** (0.94 mmol), 2-methoxy

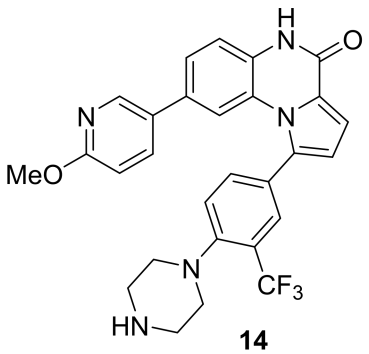
-5-pyridine boronic acid (215 mg, 1.4 mmol), $(PPh_3)_4Pd$ (150 mg, mmol) and Cs_2CO_3 (22 mg, 0.02 mmol) in DMF/H_2O (3:1, 20 mL) were heated at 80 °C under argon overnight. After the reaction was completed, it was quenched with water. The mixture was filtered, and the solid was further purified through flash chromatography (DCM/MeOH/Et_3N = 100:10:1) on silica gel to obtain a crude product which was used directly for the next step.

The obtained intermediate (0.6 mmol) and TFA (6.5 g, 60 mmol) in DCM (5 mL) were stirred at room temperature overnight. After the reaction was completed, the reaction solution was concentrated in vacuo. The pH was adjusted to 8.0 with Na_2CO_3, and the mixture was filtered, and the residue was further purified through flash chromatography (DCM/MeOH = 5:1) on silica gel to afford compound **13**/**14** as a white solid. 90% yield.



13

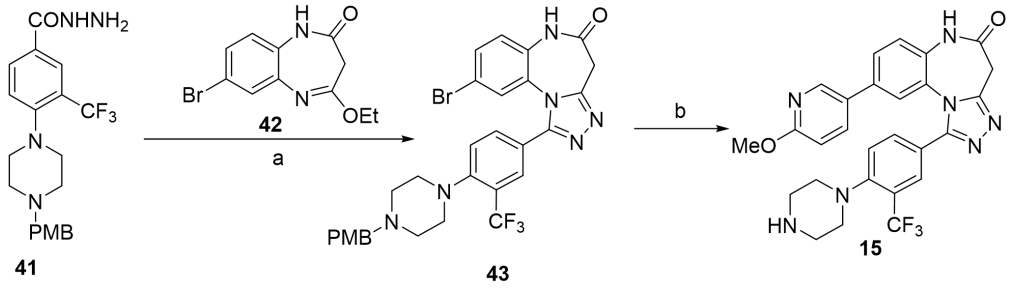
8-(6-methoxypyridin-3-yl)-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)imidazo[1,5-a]quinoxalin-4(5H)-one (13): ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (d, *J* = 2.0 Hz, 1H), 8.11 (s, 1H), 8.07 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.90-7.83 (m, 2H), 7.67 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.62 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.24 (d, *J* = 1.6 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 3.92 (s, 3H), 3.50-3.42 (m, 4H), 3.42-3.34 (m, 4H). ^{13}C NMR (100 MHz, CD_3OD) δ 165.3, 157.1, 154.3, 145.5, 145.2, 138.2, 136.5, 133.4, 131.7, 130.9, 130.5(q, *J* = 5.0 Hz), 130.4, 130.3, 129.7,126.8, 126.7 (q, *J* = 30.0 Hz), 126.6, 125.9, 123.4 (q, *J* = 271.5 Hz), 119.3, 116.1, 111.8, 54.2, 51.7, 45.4. HRMS calcd for $C_{27}H_{24}F_3N_6O_2^+$ $(M + H)^+$ 521.1907, found 521.1909. Purity 98.7% by HPLC.



14

8-(6-methoxypyridin-3-yl)-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)pyrrolo[1,2-a]quinoxalin-4(5H)-one (14): ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.45 (s, 1H), 7.89-7.82(m, 2H), 7.81-7.78 (m, 1H), 7.75-7.70 (m, 1H), 7.60-7,48 (m, 2H), 7.39-7.34 (m, 1H), 7.19-7.14 (m, 1H), 7.07-7.03 (m, 1H), 6.78-6.68 (m, 2H), 3.81 (s, 3H), 3.10-2.88 (m, 8H). ^{13}C NMR (100 MHz, DMSO-*d*$_6$) δ 162.8, 155.1, 153.2, 143.6, 136.5, 135.1, 132.2, 129.9 (q, *J* = 5.0 Hz), 129.8, 128.8, 128.5, 128.4 (q, *J* = 29 Hz), 128.1, 125.2, 123.6, 123.5,123.2 (q, *J* = 272 Hz),123.1, 117.6, 115.5, 114.0, 111.7, 110.4, 53.6, 53.1, 45.5. HRMS calcd for $C_{28}H_{24}F_3N_5O_2^+$ $(M + H)^+$ 520.1954, found 520.1935 . Purity 99.1% by HPLC.

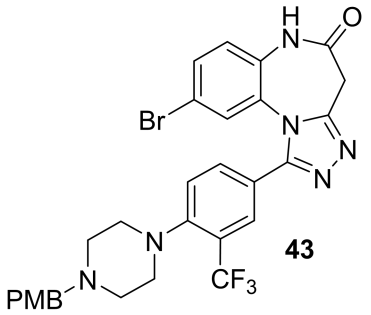
General Procedure for preparation of 15 .



Scheme 6. Syntheses of compound **15** : a) AcOH; (b) (i) TFA/TfOH = 1:1; (ii) 2-methoxy-5-pyridine boronic acid (19), $Pd(PPh_3)_4$ Cs_2CO_3, DMF/H_2O, 80 °C.

Synthesis of compound 43: Compound **41** (0.74 g, 1.76 mmol) and **42** (0.5 g, 1.76 mmol) in AcOH were heated at 120 °C for 2 h. After the reaction was completed, the reaction solution was concentrated in vacuo. The pH was adjusted to 8.0 with $NaHCO_3$, then the mixture was extracted with ethyl acetate (50 mL x 3) and washed with brine and water. The organic layer was combined, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography

(DCM/MeOH = 10:1) on silica gel to afford compound **43** as a white solid. 73% yield.

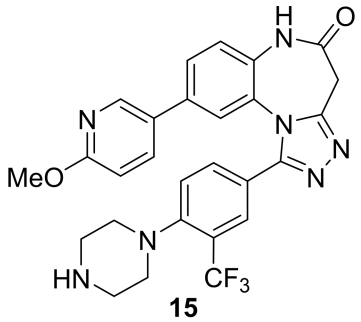


43

9-bromo-1-(4-(4-(4-methoxybenzyl)piperazin-1-yl)-3-(trifluoromethyl)phenyl)-4H-benzo[b][1,2,4]triazolo[4,3-d][1,4]diazepin-5(6H)-one (43): ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 7.70-7.62 (m, 2H), 7.61-7.55 (m, 2H), 7.31 (d, J = 8.8 Hz, 1H), 7.35-7.26 (m, 2H), 7.18 (d, J = 2.0 Hz, 1H), 6.92-6.85 (m, 2H), 3.93 (d, J = 14.4 Hz, 1H), 3.78 (d, J = 14.4 Hz, 1H), 3.74 (s, 3H), 3.46 (s, 2H), 3.34-3.30 (m, 4H), 2.96-2.90 (m, 4H).

Synthesis of compound 15: Compound **43** (0.3 g, 0.48 mmol) was dissolved in TFA (48 mmol) and TfOH (4.8 mmol), and stirred overnight at room temperature. The reaction was quenched with water, and the pH was adjusted to 8.0 with Na_2CO_3. The mixture was filtered, and the solid was further purified through flash chromatography (DCM/MeOH/Et_3N = 100:10:1) on silica gel to afford the deprotected intermediate as a white solid which was used directly for the next step.

The above product (0.4 mmol), 2-methoxy-5-pyridine boronic acid (92 mg, 0.6 mmol), $(PPh_3)_4Pd$ (9 mg, 0.008 mmol), and Cs_2CO_3 (391 mg, 1.2 mmol) in DMF/H_2O (3:1, 10 mL) were heated at 80 °C overnight under argon. After the reaction was complete, it was quenched with water. The mixture was filtered, and the solid was further purified through flash chromatography (DCM/MeOH/Et_3N = 100:10:1) on silica gel to afford compound **15** as a white solid. 47% yield.



15

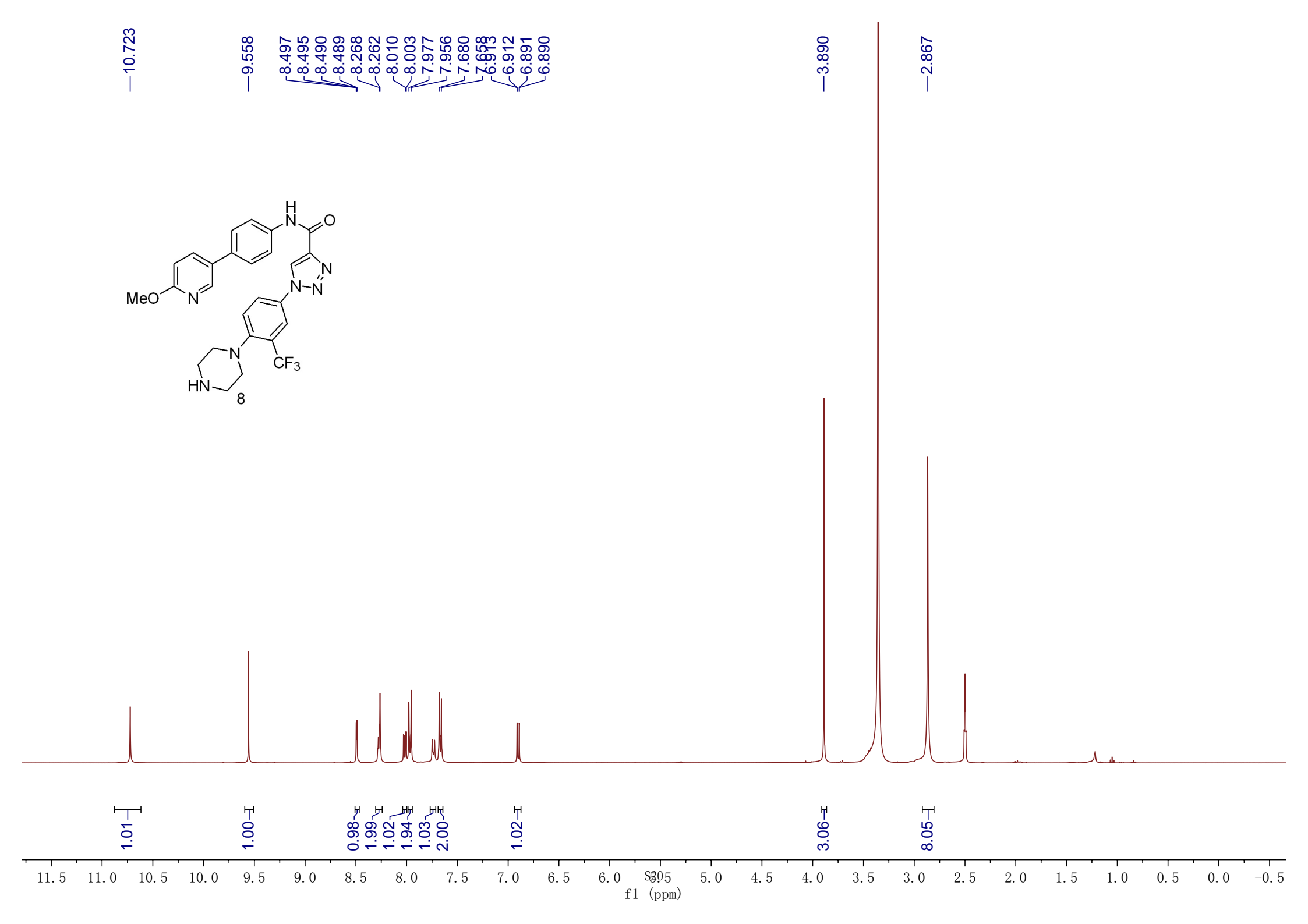
9-(6-methoxypyridin-3-yl)-1-(4-(piperazin-1-yl)-3-(trifluoromethyl)phenyl)-4H-benzo[b][1,2,4]triazolo[4,3-d][1,4]diazepin-5(6H)-one (15): ^{1}H NMR (400 MHz, CD_3OD) δ 7.83-7.85 (m, 2H), 7.80 (d, *J* = 2.4 Hz, 1H), 7.75 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.64 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 7.19 (d, *J* = 2.0 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 3.93-4.04 (m, 2H), 3.91 (s, 3H), 3.36-3.44 (m, 4H), 3.23-3.28 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD) δ 168.9, 164.4, 152.4, 152.1, 152.0, 144.7, 139.5, 137.4, 133.4, 132.3, 127.8 (q, *J* = 6 Hz), 127.7, 127.1 (q, *J* = 30 Hz), 126.5, 124.7, 124.2, 123.9, 123.4 (q, *J* = 271 Hz), 123.2, 121.4, 121.3, 119.3, 110.7, 52.9, 49.9, 43.9; HRMS calcd for $C_{27}H_{25}F_3N_7O_2^+$ $(M + H)^+$ 536.2016, found 536.2017. Purity 95.3% by HPLC.

In vitro kinases inhibition activity assays

Inhibition activities of compounds 8-15 against these kinases were determined using the FRET-based Z'-Lyte assay systems according to the manufacturer's instructions (Life Technologies, Carlsbad, CA, USA). The reactions were carried out in 384-well plates in a 10 μl of reaction volume with appropriate amounts of kinases in assay buffer. KinaseABL, FLT3 and RET's assay buffer contain 50 mM HEPES (pH 7.5), 10 mMMgCl2, 1 mMEGTA, and 0.01% Brij-35. KinaseFGFR1&2's assay buffer contain 50 mM HEPES (pH 7.5), 10 mM MgCl2, 2 mM MnCl2, 1 mM DTT, 1 mM EGTA, and 0.01% Brij-35. The reactions were incubated 1 hat room temperature in the presence of 2 μM of Peptide substrate with 10, 500, 10, 25 and 5μM of ATP for kinases ABL, FLT3, RET, FGFR1&2, respectively, and in the presence of the compounds 8-15 (1μM), then 5μl development reagent was added for further 1 hours room temperature incubation followed by the addition of 5 μl of stop solution. Fluorescence signal ratio of 445 nm (coumarin)/520 nm (fluorescein) was examined with EnVision Multilabel Reader (Perkin Elmer, Inc.). The data were analyzed using Graphpad Prism5 (GraphpadSoftware ,Inc).

Table S1: Inhibition Rate of Compounds 8- 15 (1μM) to Kinases

Inhibitory rate @ 1 μM (%)	Abl	FLT3	RET	FGFR1	FGFR2
8	9.3	17.1	0.4	-39.0	24.3
9	-1.5	22.5	1.5	-0.5	25.5
10	-2.8	29.5	3.2	-5.7	24.6
11	-2.4	12.1	1.7	0.9	24.9
12	-3.6	12.5	1.0	4.4	27.4
13	-2.1	9.4	1.3	3.7	27.1
14	-4.0	24.3	5.2	4.6	26.5
15	-0.6	-1.6	-1.6	3.9	25.9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8.497
8.495
8.490
8.489
8.268
8.262
8.010
8.003
7.977
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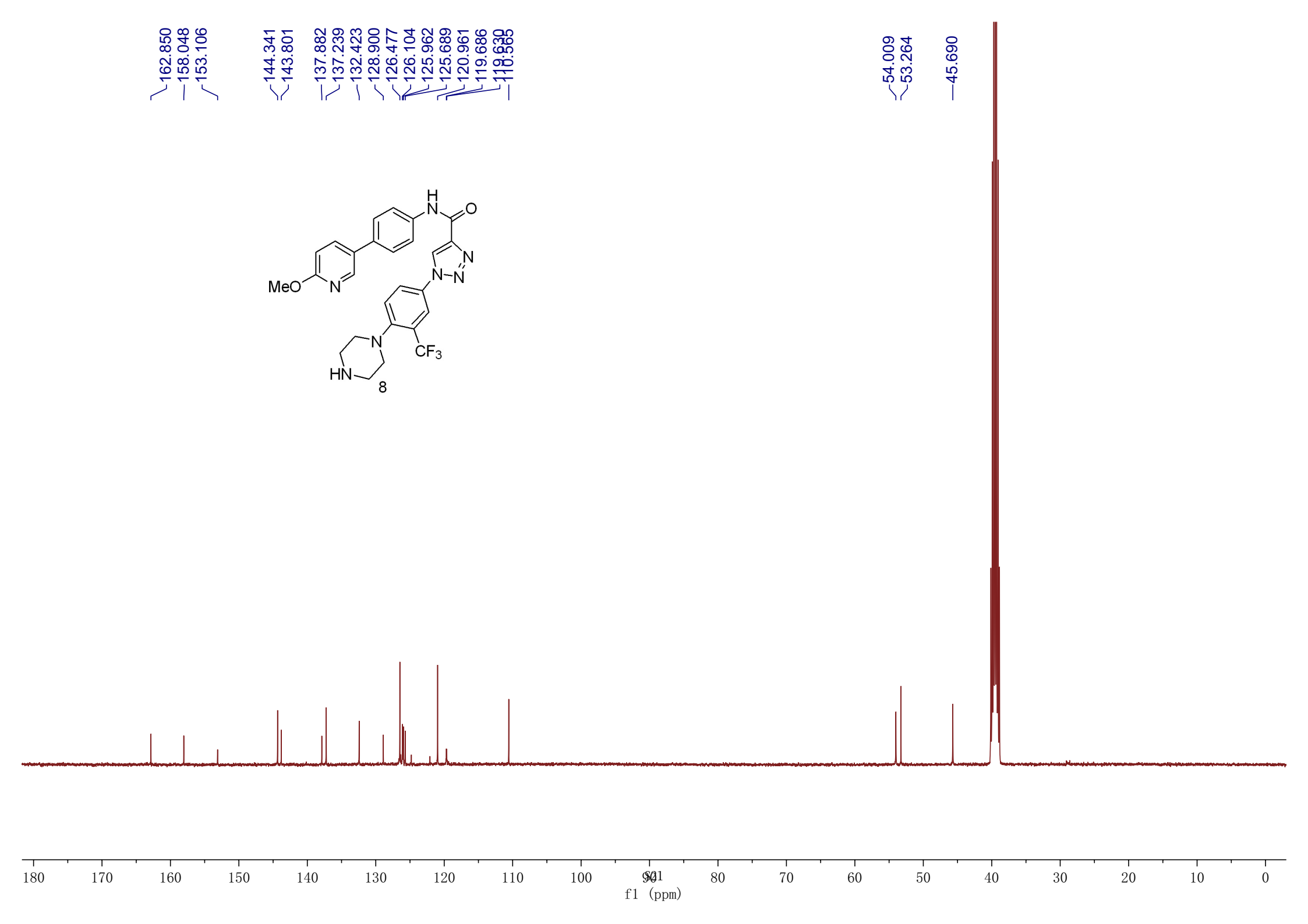
7.658
6.913
6.912
6.891
6.890
3.890
2.867
MeO
N
H
N
O
N
N
N
CF3
HN
8
1.01
1.00
0.98
1.99
1.02
1.94
1.03
2.00
1.02
3.06
8.05
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)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153.106
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143.801
137.882
137.239
132.423
128.900
126.477
126.104
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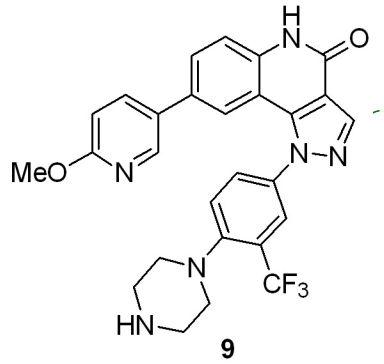
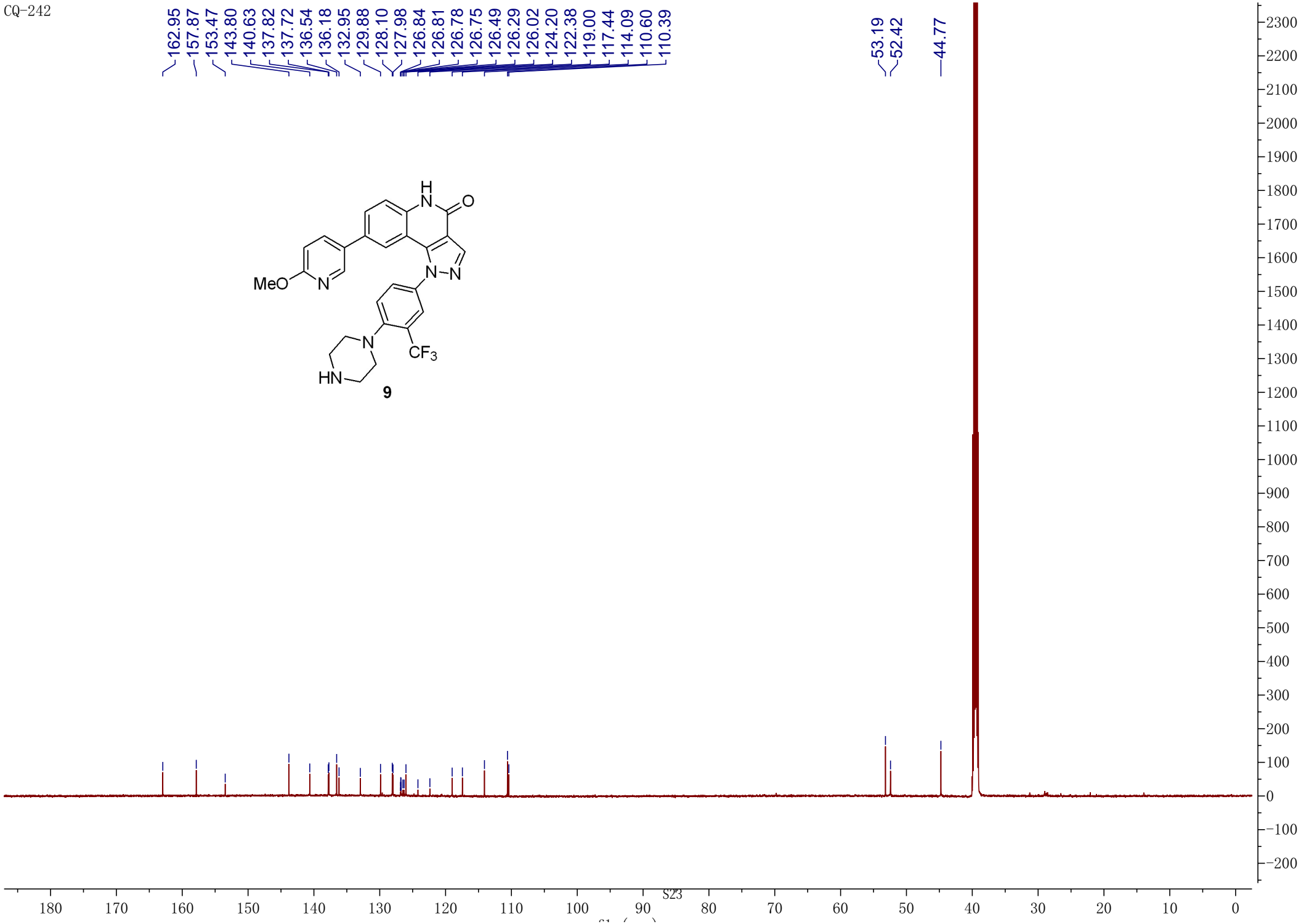
120.961
119.686
54.009
53.264
45.690
MeO
N
H
N
O
N
N
N
CF3
HN
8
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

CQ242-221014
1



9

CQ-242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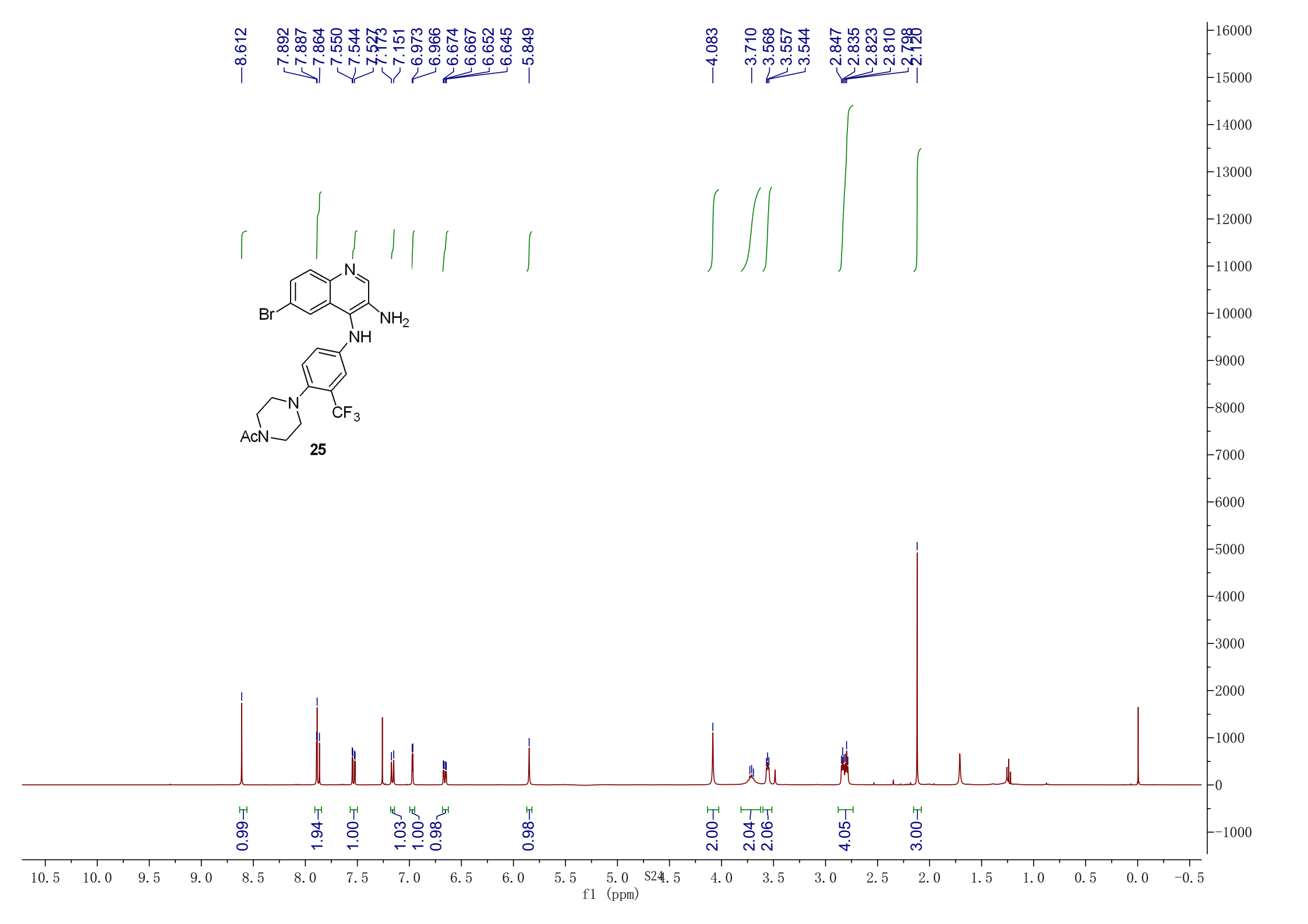
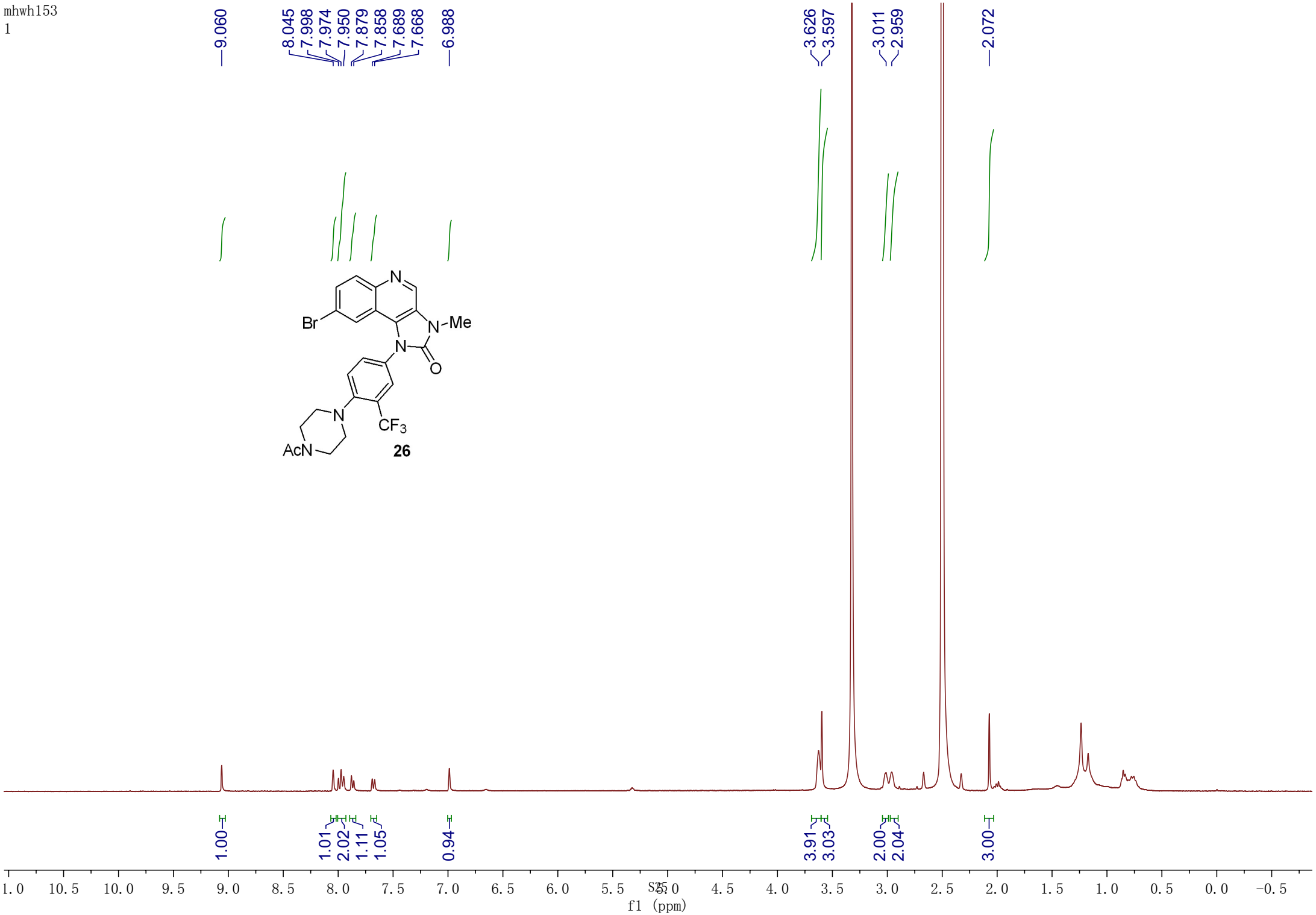
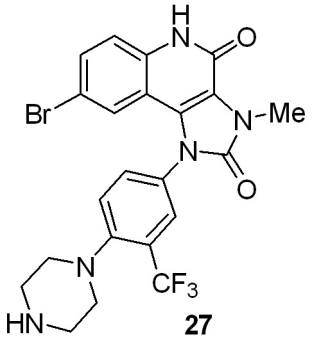
157.87
153.47
143.80
140.63
137.82
137.72
136.54
136.18
132.95
129.88
128.10
127.98
126.84
126.81
126.78
126.75
126.49
126.29
126.02
124.20
122.38
119.00
117.44
114.09
110.60
110.39
53.19
52.42
44.77
MeO
N
H
N
O
N–N
N
CF3
HN
9


8.612
7.892
7.887
7.864
7.550
7.544
7.527
7.173
7.151
6.973
6.966
6.674
6.667
6.652
6.645
5.849
4.083
3.710
3.568
3.557
3.544
2.847
2.835
2.823
2.810
2.798
2.120
Br
NH2
NH
N
CF3
AcN
25
0.99
1.94
1.00
1.03
1.00
0.98
0.98
2.00
2.04
2.06
4.05
3.00
f1 (ppm)

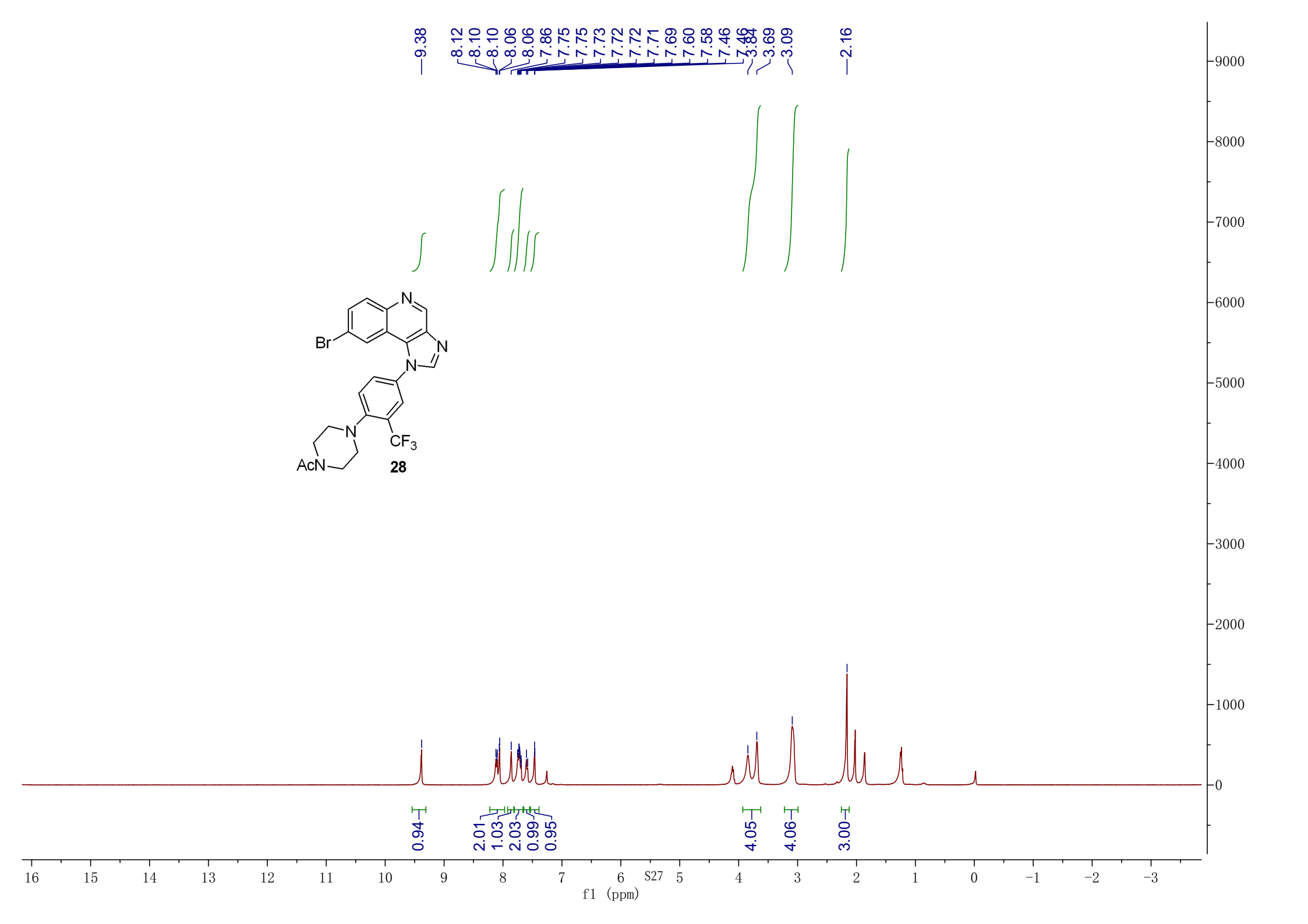
mhwh153
1


9.060
8.045
7.998
7.974
7.950
7.879
7.858
7.689
7.668
6.988
3.626
3.597
3.011
2.959
2.072
Br
N
N-Me
N
O
N
CF3
AcN
26
1.00
1.01
2.02
1.11
1.05
0.94
3.91
3.03
2.00
2.04
3.00
f1 (ppm)

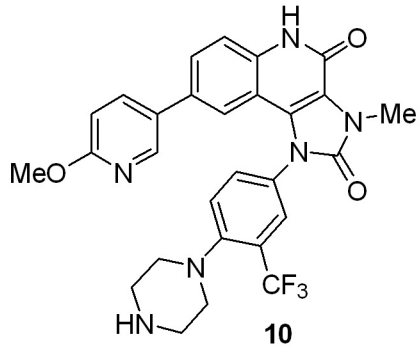
mhw-i-04-26
1



27


9.38
8.12
8.10
8.10
8.06
8.06
7.86
7.75
7.75
7.73
7.72
7.72
7.71
7.69
7.60
7.58
7.46
7.46
3.84
3.69
3.09
2.16
Br
N
N
N
N
CF3
AcN
28
0.94
2.01
1.03
2.03
0.99
0.95
4.05
4.06
3.00
f1 (ppm)

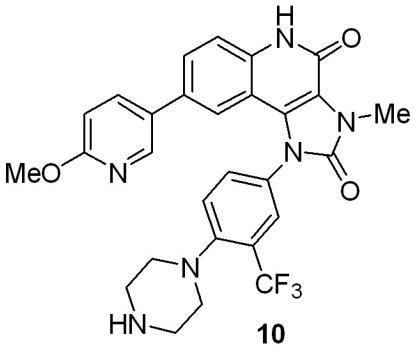
mhw-i097
1



10

f1 (ppm)

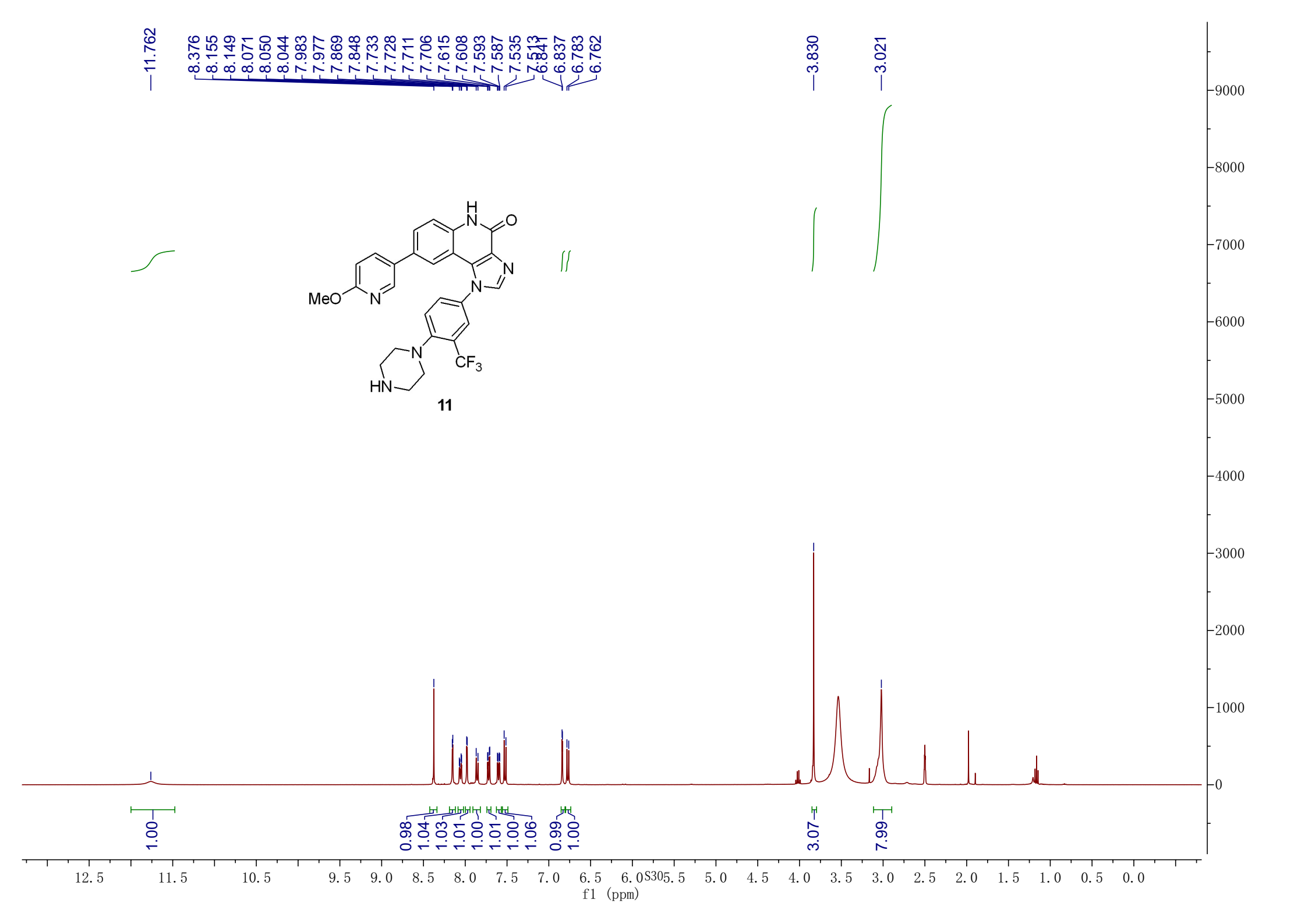
IHWI097



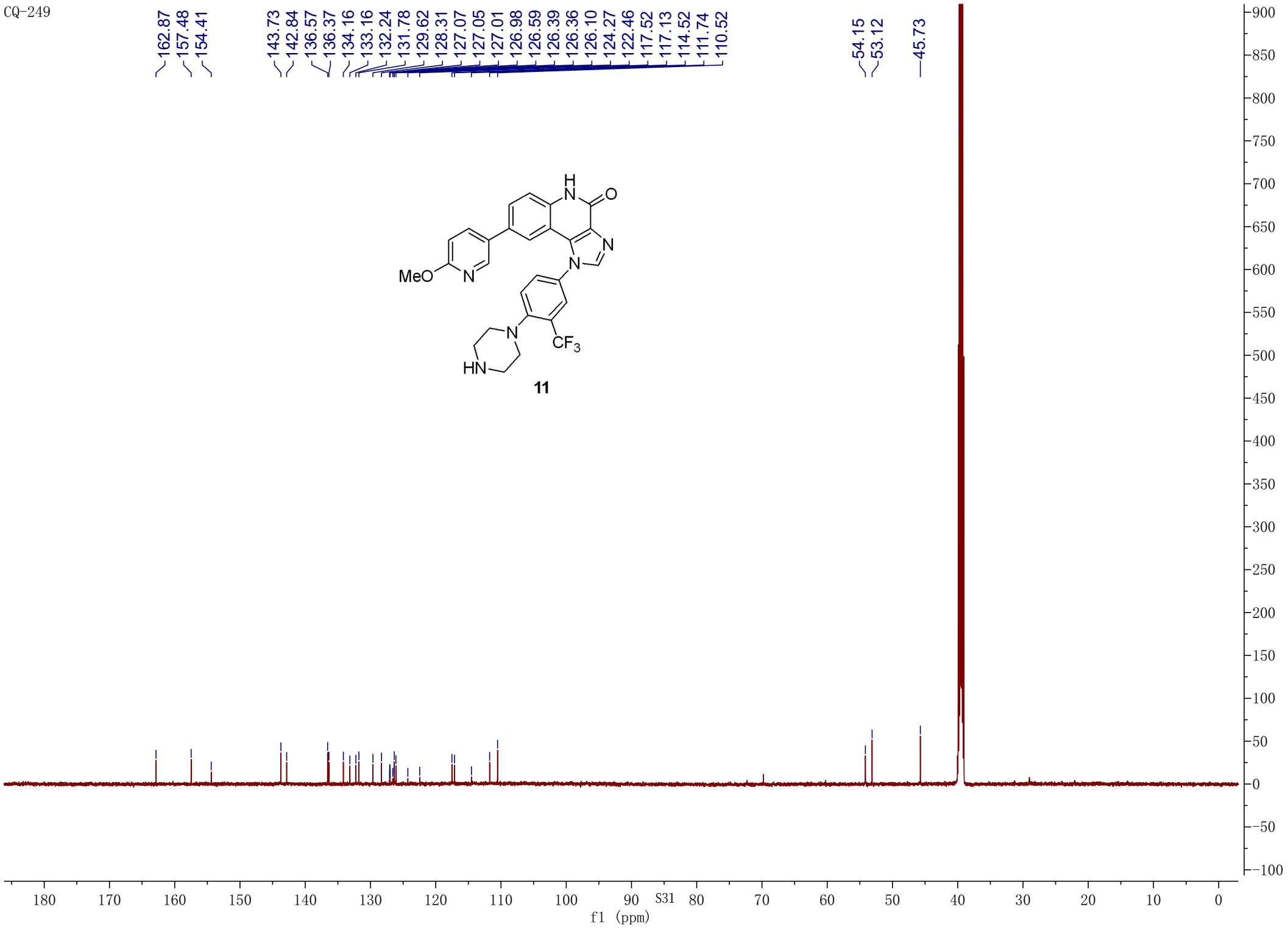
10

163.05
153.77
153.66
153.18
143.77
136.72
135.38
134.79
131.84
130.07
128.50
128.31
128.09
126.33
126.08
124.44
122.63
117.40
114.67
114.58
110.71
110.48
53.38
53.29
45.39
29.27

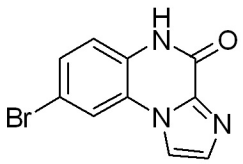
f1 (ppm)


11.762
8.376
8.155
8.149
8.071
8.050
8.044
7.983
7.977
7.869
7.848
7.733
7.728
7.711
7.706
7.615
7.608
7.593
7.587
7.535
7.513
7.511
6.841
6.837
6.783
6.762
3.830
3.021
MeO
N
H
N
O
N
N
N
HN
CF3
11
1.00
0.98
1.04
1.03
1.01
1.00
1.01
1.00
1.06
0.99
1.00
3.07
7.99
f1 (ppm)

CQ-249


162.87
157.48
154.41
143.73
142.84
136.57
136.37
134.16
133.16
132.24
131.78
129.62
128.31
127.07
127.05
127.01
126.98
126.59
126.39
126.36
126.10
124.27
122.46
117.52
117.13
114.52
111.74
110.52
54.15
53.12
45.73
MeO
N
H
N
O
N
N
N
CF3
HN
11
f1 (ppm)

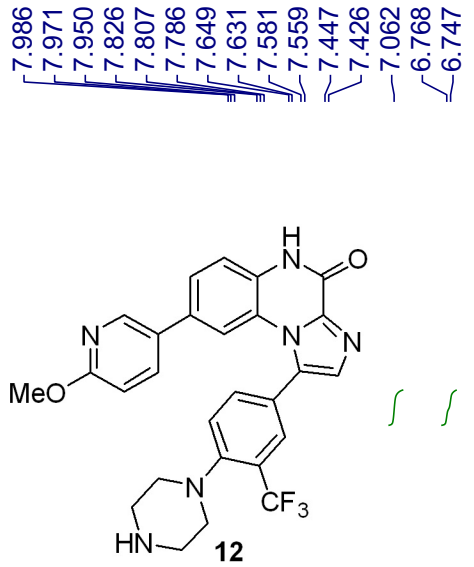
xhl-b38

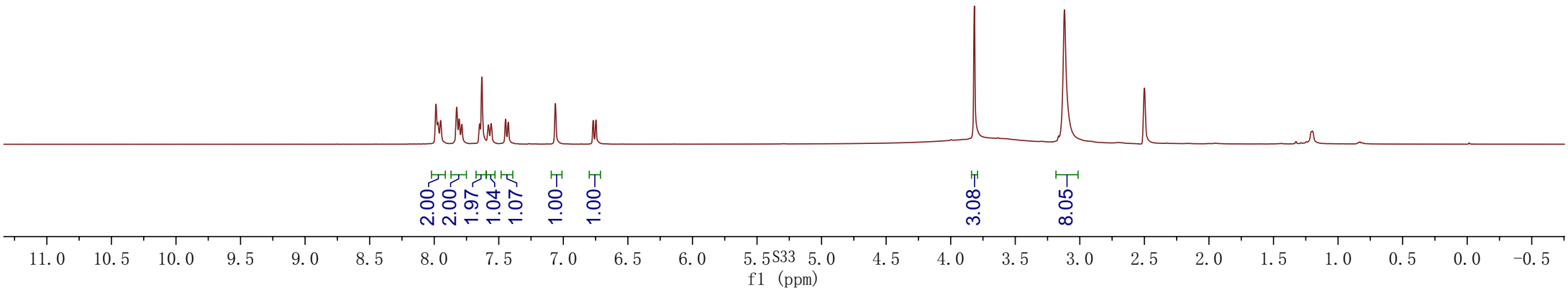

H
N
O
Br
N
N

31

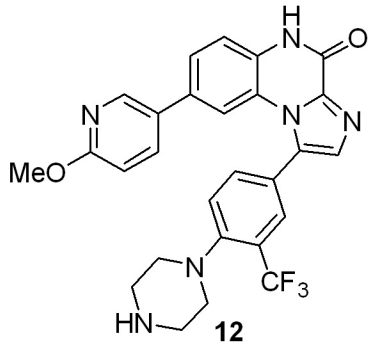
11.939
8.598
8.437
7.597
7.582
7.559
7.320
7.298
1.01
1.00
1.06
2.19
1.14
13.5
12.5
11.5
10.5
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

xh1-b47-c
1


7.986
7.971
7.950
7.826
7.807
7.786
7.649
7.631
7.581
7.559
7.447
7.426
7.062
6.768
6.747
3.816
3.119
H
N
O
N
N
N
MeO
N
CF3
HN
12


2.00
2.00
1.97
1.04
1.07
1.00
1.00
3.08
8.05
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

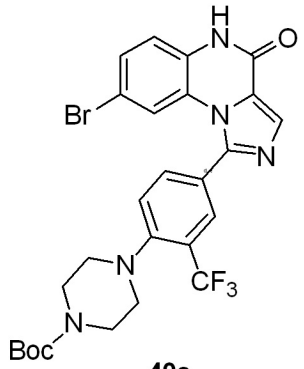
xh1-b47-c
1


H
N
O
N
N
N
MeO
N
CF3
HN

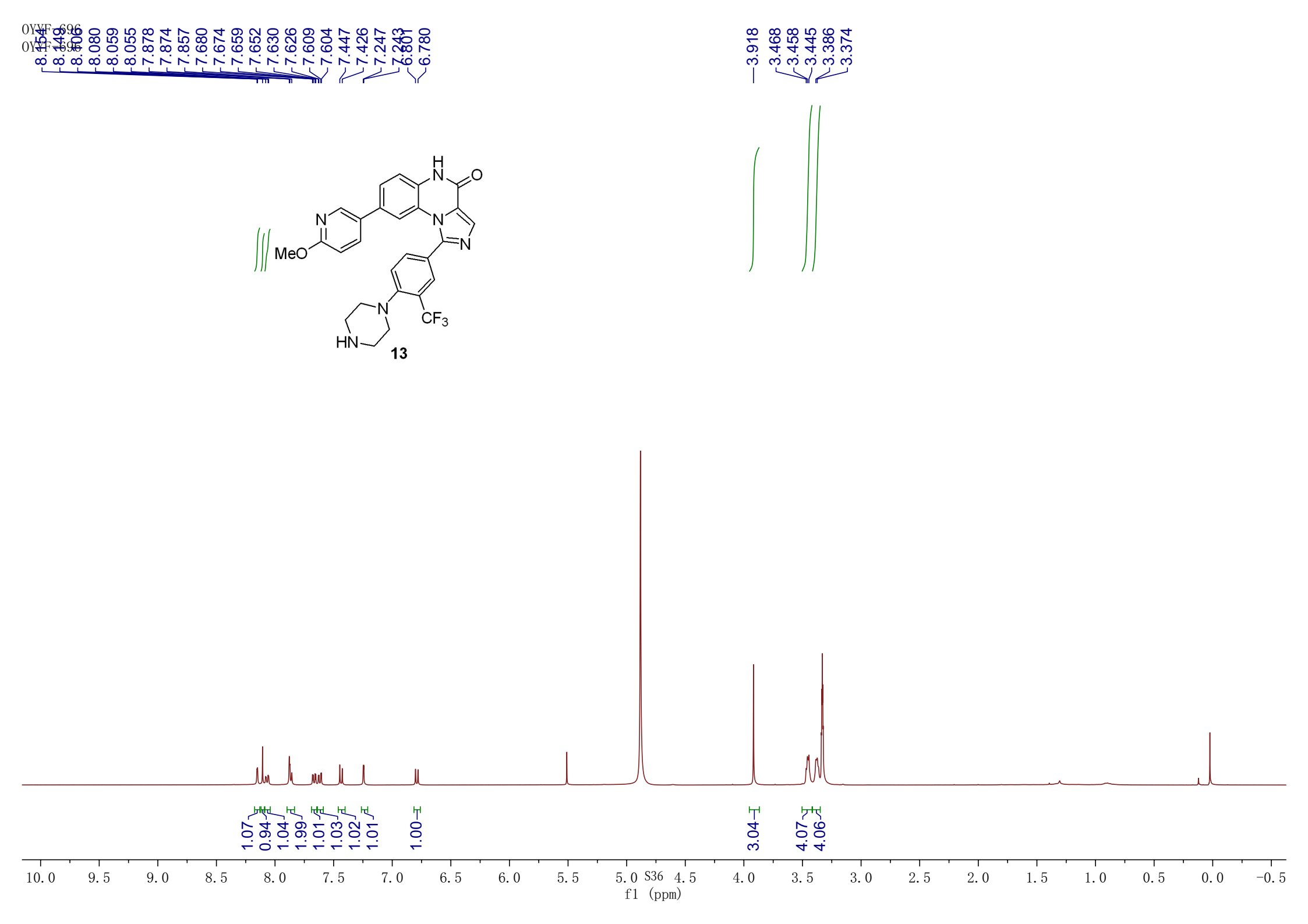
12

163.00
152.92
152.60
143.68
136.54
133.19
130.25
128.57
127.78
126.96
125.32
124.36
122.98
117.67
113.57
110.58
53.13
51.95
44.60
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

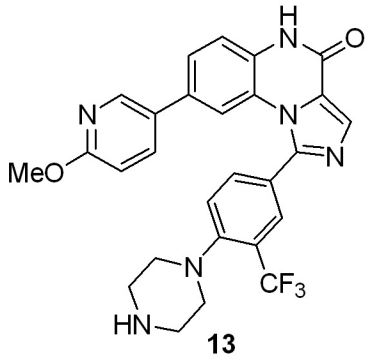
0YYF-690-1
0YYF-690-1



40a


0YYF-696
0YYF-696
8.154
8.149
8.106
8.080
8.059
8.055
7.878
7.874
7.857
7.680
7.674
7.659
7.652
7.630
7.626
7.609
7.604
7.447
7.426
7.247
7.243
6.801
6.780
3.918
3.468
3.458
3.445
3.386
3.374
MeO
N
N
N
N
H
O
CF3
HN
13
1.07
0.94
1.04
1.99
1.01
1.03
1.02
1.01
1.00
3.04
4.07
4.06
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

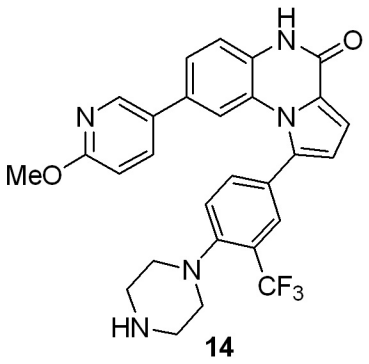
0YYF-696



13

165.27
157.06
154.25
145.45
145.18
138.22
136.48
133.44
131.72
130.88
130.52
130.48
130.45
130.29
129.71
129.36
129.14
126.75
126.62
125.94
123.44
119.25
116.06
111.76
54.15
51.65
45.44

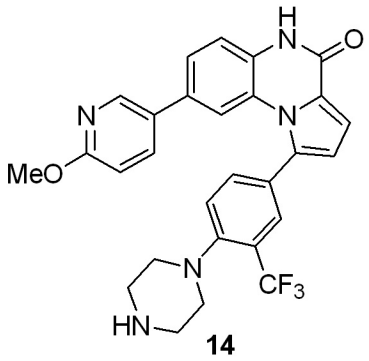
xh1-b20



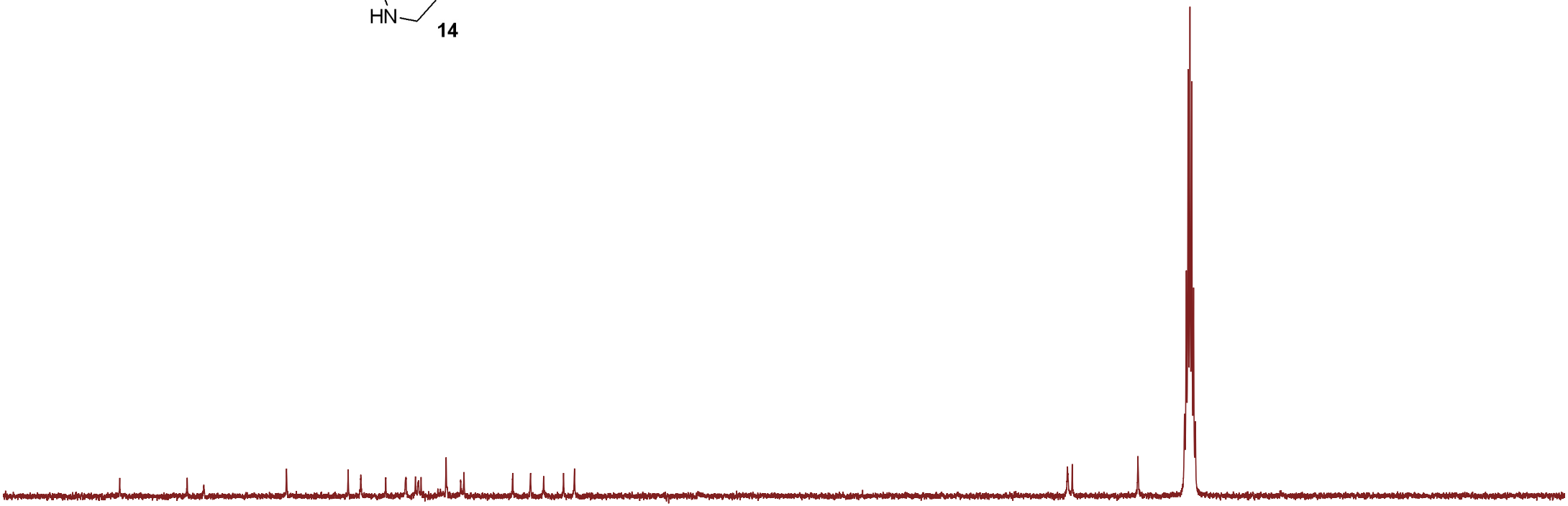
14

XHL-B20-CC
1

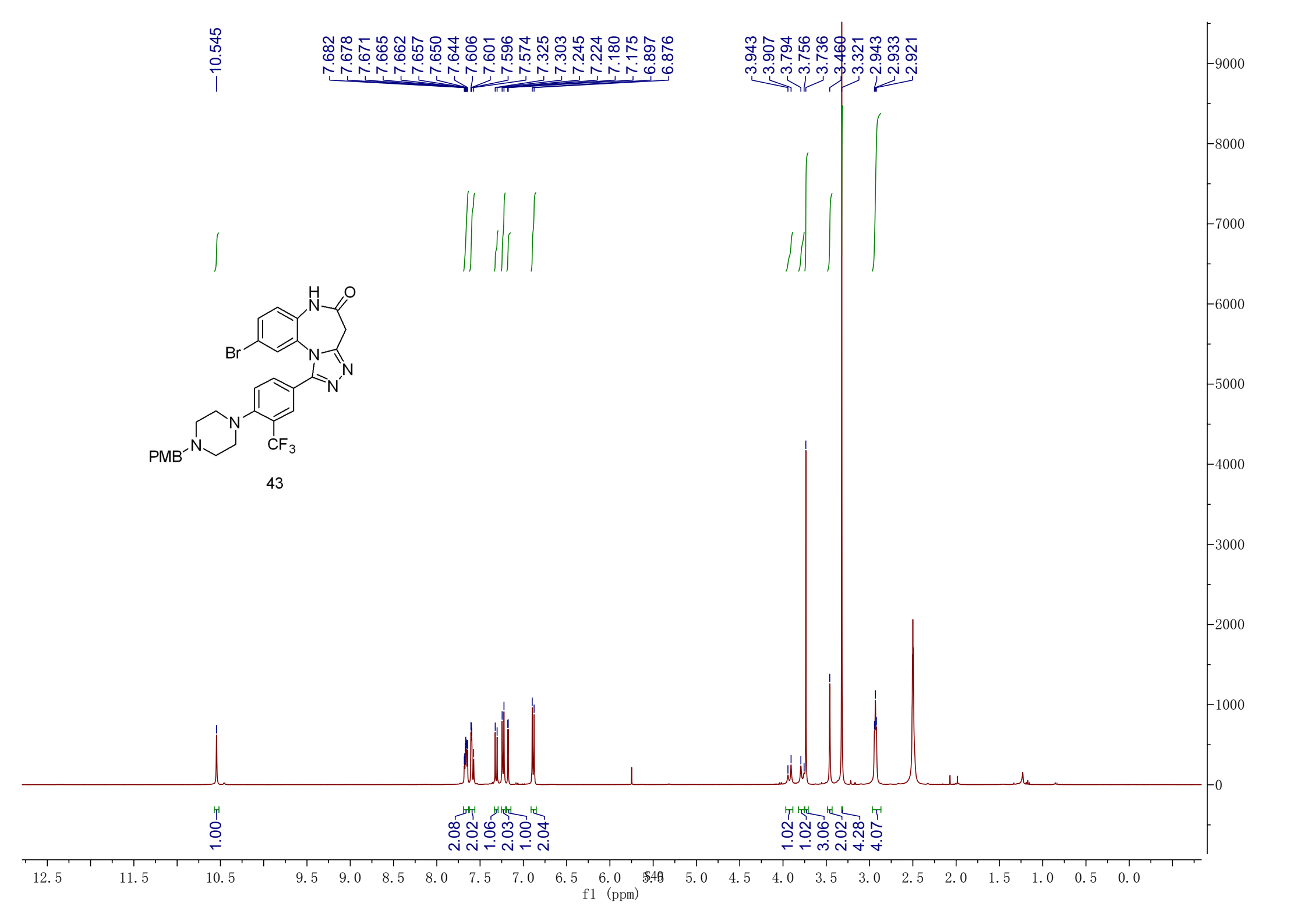
162.84
155.07
153.15
143.63
136.52
135.06
129.86
128.76
128.12
125.23
123.18
123.17
117.56
115.50
113.98
111.70
110.43
53.61
53.07
45.50

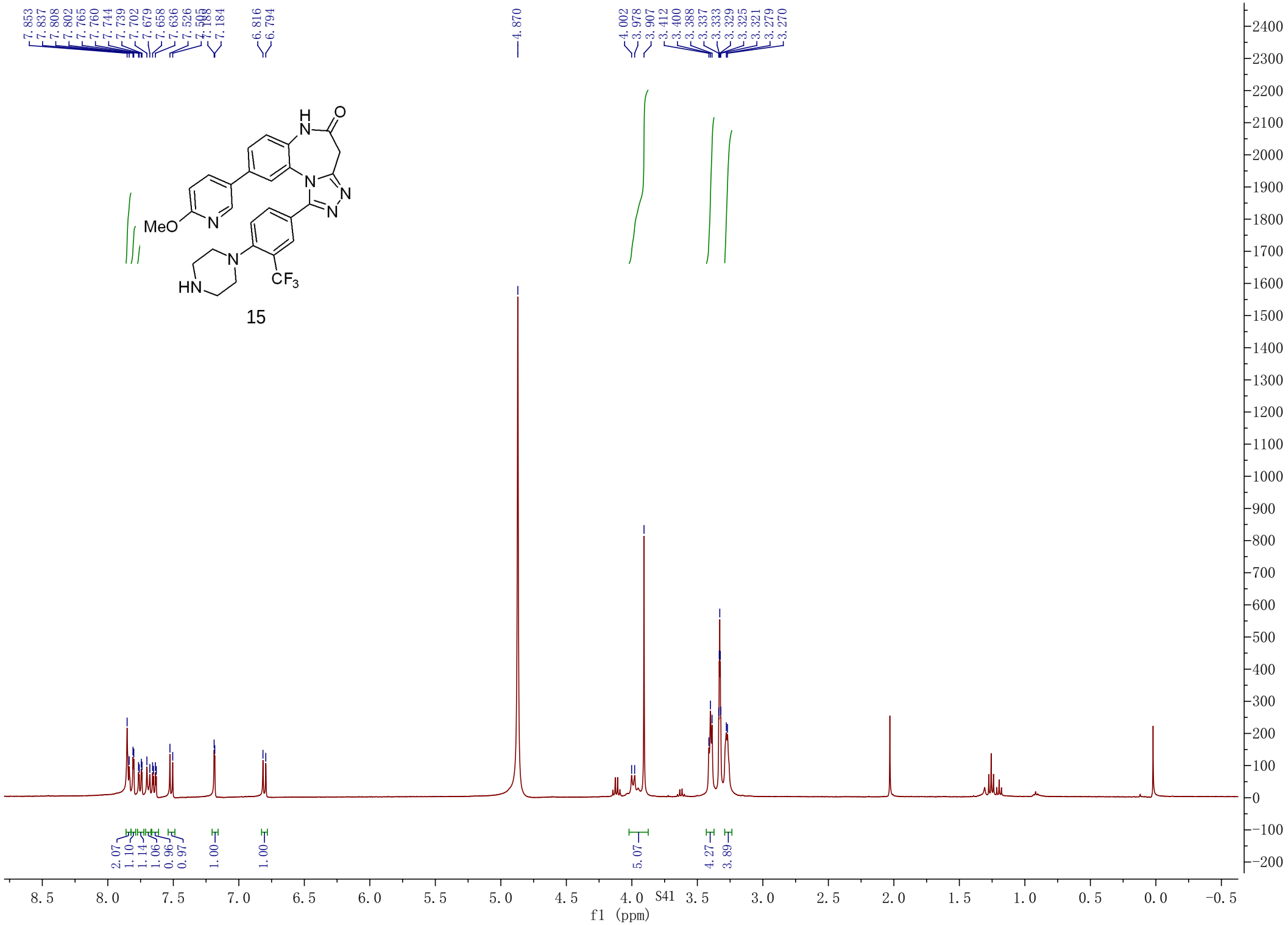


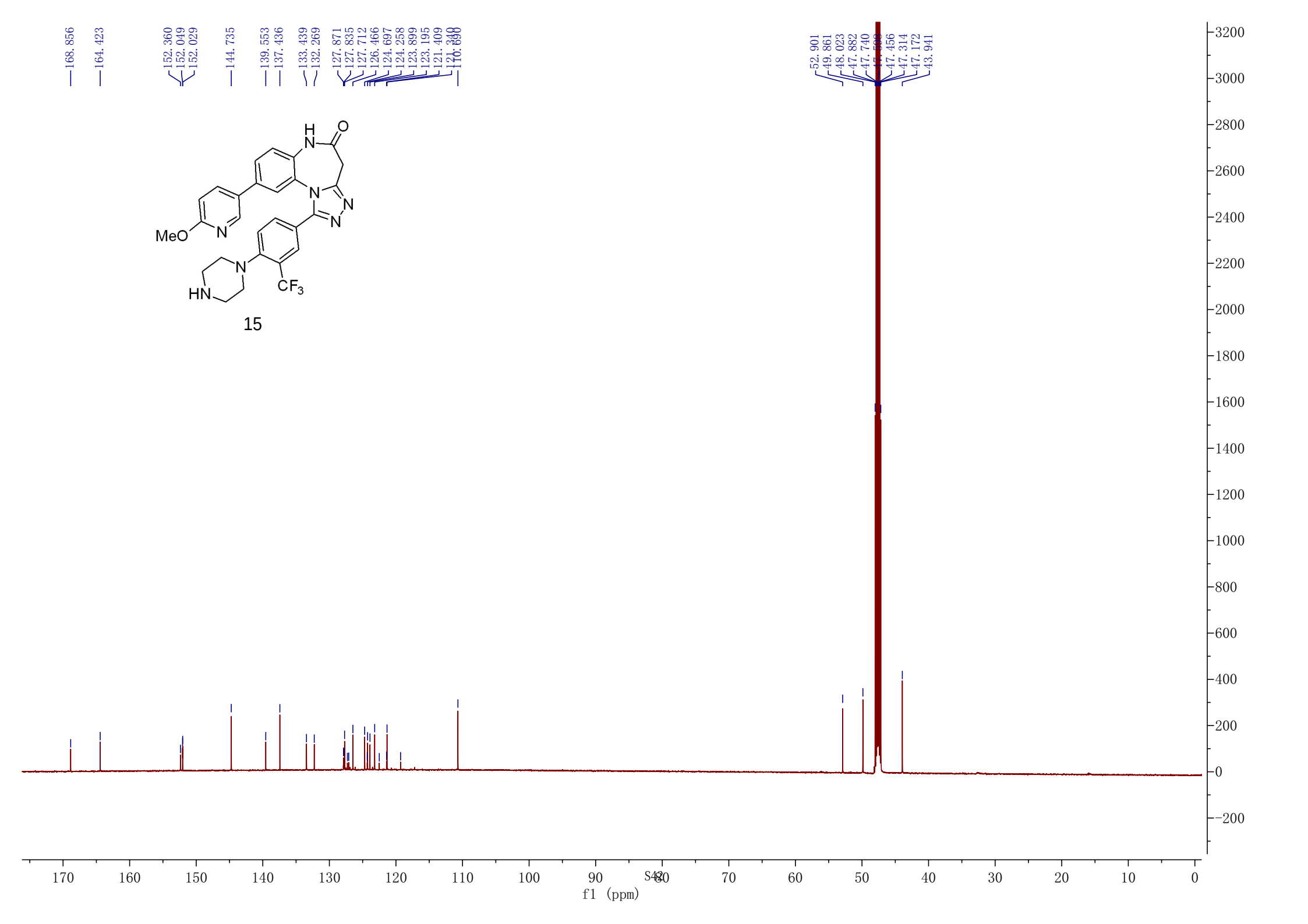
14



f1 (ppm)


10.545
7.682
7.678
7.671
7.665
7.662
7.657
7.650
7.644
7.606
7.601
7.596
7.574
7.325
7.303
7.245
7.224
7.180
7.175
6.897
6.876
3.943
3.907
3.794
3.756
3.736
3.460
3.321
2.943
2.933
2.921
Br
N
O
H
N
N
N
N
PMB
CF3
43
1.00
2.08
2.02
1.06
2.03
1.00
2.04
1.02
1.02
3.06
2.02
4.28
4.07
f1 (ppm)


7.853
7.837
7.808
7.802
7.765
7.760
7.744
7.739
7.702
7.679
7.658
7.636
7.526
7.505
7.188
7.184
6.816
6.794
4.870
4.002
3.978
3.907
3.412
3.400
3.388
3.337
3.333
3.329
3.325
3.321
3.279
3.270
MeO
N
N
N
N
H
O
N
HN
CF3
15
2.07
1.10
1.14
1.06
0.96
0.97
1.00
1.00
5.07
4.27
3.89
f1 (ppm)
S41


168.856
164.423
152.360
152.049
152.029
144.735
139.553
137.436
133.439
132.269
127.871
127.835
127.712
126.466
124.697
124.258
123.899
123.195
121.409
52.901
49.861
48.023
47.882
47.740
47.456
47.314
47.172
43.941
MeO
N
HN
CF3
O
H
15
f1 (ppm)